CATALYTIC OXIDATION OF ORGANIC SUBSTRATES USING TRANSITION METAL COMPLEXES

BY

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This thesis is dedicated to my parents, Michael and May Lo.

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The oxidation of organic substrates is an important class of chemical transformations that has utility in a variety of industrial processes and in fine chemical production. Catalysis plays an important role in oxidation chemistry, giving a cleaner environment through the destruction of pollutants and the development of cleaner industrial processes.

The work presented in this dissertation is divided into two major sections. The first systems discussed will be zeolite-encapsulated transition metal complexes that employ shape selectivity to control reaction pathways of saturated hydrocarbon oxidations. The goal was to design effective heterogeneous catalysts for the conversion of cyclohexane and cyclohexane derivatives to adipic acid. Adipic acid is an industrially important compound

and present industrial production raises environmental concerns. Finding an alternative system for synthesizing adipic acid to address these environmental concerns is the major motive for this research.

The second section focuses on the development and utilization of chiral transition metal complexes that were used in stereoselective epoxidations of nonfunctionalized olefins. The goal in this case was to find effective enantioselective catalysts that are easily synthesized. The production of chiral molecules has great significance in pharmaceutical applications and natural products synthesis.

CHAPTER 1
INTRODUCTION TO CATALYTIC OXIDATION CHEMISTRY

Oxidation chemistry, in its broadest sense, is defined as a process in which the oxidation state of an element increases. In organic transformations, oxidation is used to describe an increase in the number of oxygen atoms bound to a carbon atom. The oxidation of organic substrates is an important class of chemical transformations that has utility in a variety of industrial processes and in fine chemical production.

The oxidation of organic compounds has been known since the nineteenth century where early investigators observed that the reaction of oxygen with many organic materials resulted in the deterioration of these compounds. In the early twentieth century, these oxidative processes were found to involve the formation of organic peroxides. In the middle of this century, mechanistic studies of the interaction of dioxygen with hydrocarbons suggested evidence for the free radical chain theory of autoxidation. The autoxidation mechanism is shown in Figure 1-1. Various studies of the autoxidation of hydrocarbons have shown that radicals play an important role in a chain reaction type mechanism.[3-7]

Initiation

a) $In_2 \longrightarrow 2In\cdot$

b) $In\cdot + R\text{-}H \longrightarrow In\text{-}H + R\cdot$

Propagation

c) $R\cdot + O_2 \longrightarrow RO_2\cdot$

d) $RO_2\cdot + R\text{-}H \longrightarrow RO_2H + R\cdot$

Termination

e) $R\cdot + RO_2\cdot \longrightarrow RO_2R$

f) $R\cdot + R\cdot \longrightarrow R\text{-}R$

g) $2RO\cdot \longrightarrow [ROOOOR] \longrightarrow R{=}O + ROH + O_2$

Figure 1-1. Autoxidation scheme via chain radical mechanism.

Radicals may be generated by an initiator, such as heat or light, or alkyl peroxides that are easily homolytically cleaved can act as an initiator to generate radicals.[3] Thermal decomposition of alkyl hydroperoxides is a major generator of radicals in autoxidation reactions. The initiator abstracts a hydrogen radical from the substrate, as shown in reaction b) in Figure 1-1, to yield an alkyl radical. Initiation by the direct reaction of dioxygen with hydrocarbons is generally not kinetically favorable, although there are some cases in which this is observed.[8-12] This case may be explained by the presence of radicals formed by the decomposition of peroxide impurites present in the substrate.[10]

The addition of an alkyl radical to oxygen to form an alkyl peroxy radical is an extremely rapid process.[13] Shown in reaction c) in Figure 1-1, the alkyl peroxy radical abstracts a hydrogen atom from a substrate molecule to produce the alkyl hydroperoxide and an alkyl radical. The alkyl radical reacts with dioxygen and the propagation cycle starts again, as in reaction d). At partial pressures of oxygen in excess of 100 torr, the rate determining step is hydrogen transfer from the substrate to the alkyl peroxy radical.[12] If the ROO-H bond strength is as strong as the R-H bond, oxidations are likely to be rapid.[13] The ROO-H bond has been estimated to be about 90 kcal/mol, which is larger than an allylic or benzylic C-H bond (about 85 kcal/mol) and comparable to a tertiary C-H bond of a saturated hydrocarbon.[14-15] With this in mind, alkyl peroxy radicals are selective and preferentially abstract only the most weakly bound hydrogen atoms. Alkyl peroxy radicals are relatively stable and have selectivity

similar to bromine radicals. It has been shown that the relative rates of attack at the primary, secondary and tertiary C-H bonds of 2-methylpentane increase in the order of 1:30:300.[14,15] Studies of these rate constants on the autoxidations of various substrates have indicated that the reactivities are strongly dependent on the structure of the alkyl peroxy radicals, with the major influences coming from steric and polar effects.[16-19]

Radical recombinations are possible in autoxidations, as shown by the termination steps in Figure 1-1. One interesting termination reaction involves the self dimerization of alkyl peroxy radicals to form a tetraoxide intermediate. This intermediate has never been isolated, but it is thought to undergo disproportionation to form an alcohol, a carbonyl compound, and dioxygen as shown by reaction g) in Figure 1-1.[20,21]

In autoxidation reactions, hydroperoxides are usually the major products, and can be isolated in high yields. One of the most well known commercial processes is the conversion of cumene to cumene hydroperoxide, which is normally reacted further to give phenol and acetone.[22] Another important system involves the liquid-phase autoxidation of isobutane that yields 75% tertiary butyl hydroperoxide and 21% tertiary butyl alcohol.[23] Hydroperoxides are excellent oxidant sources to mediate other oxidative transformations of organic substrates.

The controlled oxidation of hydrocarbons and other organic compounds is important for the direct synthesis of oxygen-containing compounds. This type

of control may be achieved by changing the medium in which the oxidation is carried out to give the desired product or products. One way to implement this control is through the rational selection of solvent.[24] There have been extensive studies on the role of solvation on the chemical kinetics of heterolytic reactions and homolytic reactions.[25-29] Two modes of solvation, non-specific and specific, have been recognized and studied.[30-37]

It is well known that oxidation in vapor phase and liquid phase constitutes the most important area of chemical production of petrochemical products from hydrocarbons. In the past 50 years, many vapor phase syntheses have been converted to liquid phase. This trend has led to many economic advantages, including greater selectivity, greater overall yield, less severe conditions, and better manageability of equipment.[38]

A thermodynamically favorable reaction may be slow at modest temperatures and has little synthetic value. Increasing the temperature may accelerate the reaction rate, but this may be expensive and higher temperatures may induce competing side reactions. Another approach to increasing reaction rates is by the use of a catalyst. The general definition of a catalyst is an agent added to a chemical reaction that increases the rate of reaction but is not itself consumed. A catalyzed reaction is faster than an uncatalyzed reaction because the catalyst provides a different reaction pathway with lower activation energy. There are several ways to express the rate of a catalyzed reaction. Catalytic

efficiency is described by the turnover frequency or turnover number, N. In a reaction that converts X to Y catalyzed by C with a rate of v,

$$A \longrightarrow B \tag{1-1}$$

$$v = d[A]/dt \tag{1-2}$$

and the turn over frequency is given by

$$N = v/[C], \tag{1-3}$$

if the rate of the uncatalyzed reaction is negligible. A very active catalyst induces fast reaction rates even at low temperatures, and has a high turn over frequency. Catalysts play an increasing role in achieving a cleaner environment, both through the destruction of pollutants and through the development of cleaner industrial processes with less abundant byproducts.

Catalysts are classified into two categories: homogeneous and heterogeneous. A homogeneous catalyst is soluble in the reaction medium in which the reaction mixture exists in one phase. In contrast, catalysts are heterogeneous if they are present in a phase different from that of the reaction medium. Each type has its own advantages and disadvantages. Homogeneous catalysts operate at low temperatures and pressures, give good selectivity, but are usually difficult to separate from the reaction products. Heterogeneous catalysts are easily separated from the reaction products but require high temperatures and pressures and give poor selectivity.

In heterogeneous catalysis, the reaction rate is normally expressed in terms of the rate of change in the formation of product, rather than

concentration. The determination of active sites in a heterogeneous catalyst is a challenging problem and the denominator [C] in Equation 1-3 is usually replaced by the surface area of the catalyst.

Although increasing a reaction rate of a catalytic reaction is important, other criteria that an effective catalyst must meet are good selectivity and long catalytic lifetime. Catalysts that are selective induce the formation of the desired product in high percentages and minimize the amount of side products. For example, poor selectivity occurs when the metallic silver-catalyzed oxidation of ethylene with molecular oxygen gives ethylene oxide as the desirable product, but also gives significant amounts of the more thermodynamically favored but less desirable formation of carbon dioxide and water.[39]

Transition metal complexes are often employed in catalytic oxidation of organic substrates, where the transition metal atom alternates between two or more oxidation states. Many review articles and books have been written in this area.[14,40-58] These catalytic processes generally have advantages over their noncatalytic counterparts by proceeding under milder conditions, and they may be more selective towards the desired products. More specifically, catalysis plays an important role in the selective and partial oxidation of alkanes, olefins, and aromatic compounds. A large portion of commercial petrochemical processes involve catalysis, and catalytic oxidations are arguably one of the more important ones.

Often a catalytic transition metal complex does not interact with either dioxygen or the hydrocarbon. Many metal complexes that bind molecular oxygen have been isolated and characterized, but they are not involved in the major oxidation pathways.[40] The reaction between oxygen and hydrocarbons is a radical chain process in these cases, and even occurs in the absence of transition metal catalysts. Transition metal complexes may cause catalytic decomposition of the hydroperoxides formed through autoxidation of the hydrocarbon. In other cases, catalysis by transition metal complexes generally enhances the formation of desirable oxidation products from oxygen by allowing control over the yield and the rate of the oxidation process.

Some major applications of industrial oxidations of hydrocarbons is shown in Table 1-1. An important industrial oxidation is used in the synthesis of

Table 1-1.[39] Industrial Oxidations of Hydrocarbons.

Hydrocarbon	Oxidation Product	Applications
Cyclohexane	Cyclohexanol and Cyclohexanone	Converted to adipic acid and caprolactam (nylon precursors)
Cyclododecane	$C_{12}H_{23}OH$ and $C_{12}H_{22}O$	Oxidized to dodecanedioic acid and lauryl lactam (polyamide precursors)
Butane	Acetic acid	Solvent, vinyl acetate polymers, maleic anhydride
Toluene	Benzoic acid	Phenol synthesis
m-Xylene	Isophthalic acid	Polymers and plasticizers
p-Xylene	Terephthalic acid and terephthalate esters	Polyester fibers, films, and plastics

adipic acid, which is a major intermediate in the production of nylon 6,6. Adipic acid synthesis will be a major focus in this dissertation.

Five fundamental steps account for most of the homogeneous catalytic cycles in hydrocarbon transformations. Catalysis involving ligand coordination and dissociation usually requires facile coordination of reactants to the active metal center and facile dissociation of products. These labile complexes contain an open coordination site or a site that is weakly coordinated, and are called coordinatively unsaturated. Sixteen electron complexes that are square planar are coordinatively unsaturated, and they are often used in catalysis of organic substrates.

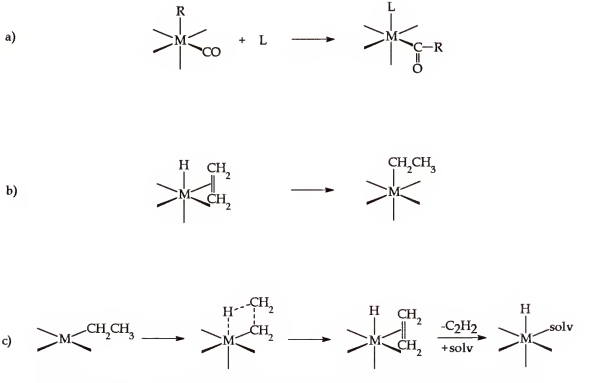

Figure 1-2.[40] Typical catalytic insertion and elimination mechanisms.

Insertion and elimination catalysis occurs through various mechanisms as shown in Figure 1-2. Alkyl and hydride ligands can migrate to unsaturated ligands, which is also called a migratory insertion reaction, as shown in Figure 1-2 a). A variation of this is the migration of a hydrogen atom to a coordinated alkene to produce a coordinated alkyl ligand, as shown in Figure 1-2b). The reverse process of insertion is elimination, which includes β-hydrogen elimination, shown in Figure 1-2 c).

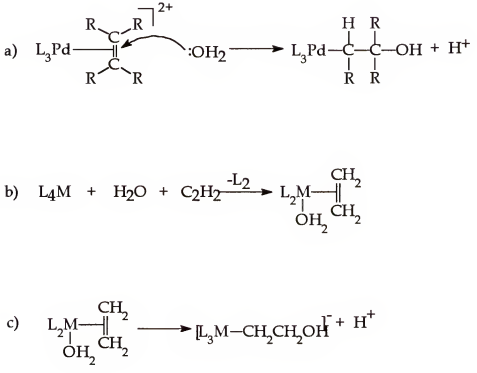

Figure 1-3.[40] Nucleophilic attack of water on coordinated alkenes.

Catalysis also occurs by the nucleophilic attack on coordinated ligands.[40] This occurs when a ligand such as CO or an alkene is activated toward nucleophilic attack by coordination to transition metal ions in positive oxidation states. The hydration of an alkene bound to palladium(II) is a good example of this type of chemistry, as shown in Figure 1-3 b). The nucleophilic attack occurs on the most highly substituted carbon atom of the coordinated alkene, since this carbon forms the most stable pseudo-carbocation.

Oxidative addition and reductive elimination is shown in Figure 1-4.[40] The oxidative addition of a molecule AB to a square planar transition metal complex causes the dissociation of the A-B bond and coordination of the two fragments to the metal center. Reductive elimination is simply the reverse of oxidative addition. It often follows oxidative addition and insertion reactions in the catalytic cycle. Mechanisms of oxidative additions vary and depend on the reaction conditions and the nature of the reactants.

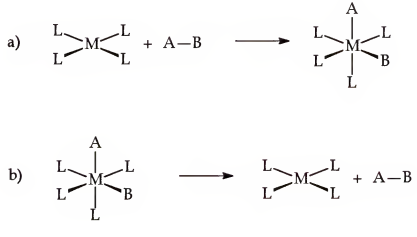

Figure 1-4.[40] Oxidative addition and reductive elimination.

The various reaction pathways available in transition metal catalyzed oxidation led to a classification scheme to describe the role of the transition metal complex.[59,60] In this classification scheme, five classes of oxidation reactions were proposed.

Class I metal catalyzed reactions involve complexes that reversibly bind molecular oxygen. Examples include the conversion of allyl substituted phenols to quinones, the oxidation of flavanols to carbon monoxide and ring-opened products, and the conversion of isoeugenol and lignosulfonate converted to vanillin.[61-63] The coordination of molecular oxygen to transition metals is described by the spin pairing model, which explains how the coordination affects the basicity and radical character of the oxygen.[64-67]

Class II oxidations involve the formation of metal-oxo species by the reaction of a metal with molecular oxygen. Oxidation of alkanes by metal oxo complexes occurs by various pathways that depend on the acceptor properties of the metal oxo bond.[57] When the metal-oxo exhibits little electrophilicity, oxidation occurs via hydrogen abstraction, as shown in Figure 1-5A. When the metal oxo bond shows great electrophilicity, the oxygen atom is inserted between the C-H bond, as shown in Figure 1-5B.

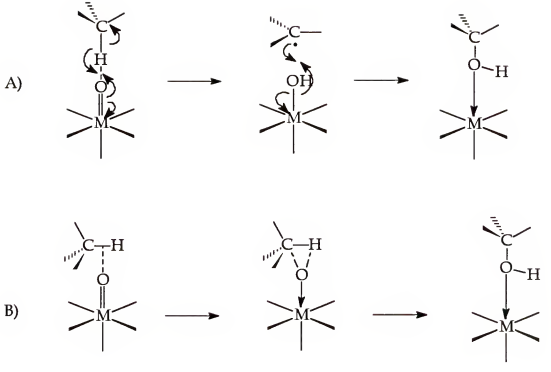

Figure 1-5.[57] Oxidation pathways for alkanes via Class II type reactions.

Class III reactions involve the formation of metal-oxo species via peroxides. Transition metal catalysts in this class generally are not easily oxidized to a high oxidation state with molecular oxygen since it is thermodynamically or kinetically unfavorable. With stronger oxidants such as hydrogen peroxide and alkylhydroperoxides, either a two electron-two proton transfer or an oxygen transfer occurs between the metal center and the peroxide. The resulting metal-oxo species can then be utilized in the oxidation of organic substrates. Generally, metals that have stable oxidation states that differ by two are likely candidates of forming metal-oxo species via peroxides.

Class IV reactions involve metal peroxo complexes as reactive intermediates. They are generated by the reaction of transition metals with alkylhydroperoxides or hydrogen peroxide. This normally occurs with metals that have two stable oxidation states that differ by one, which is the criterion that differentiates the formation of a metal-peroxo species as opposed to the formation of a metal-oxo discussed in Class II and Class III reactions. There are two main steps that constitute Class IV reactions. The first step is the metal catalyzed formation of an alkylhydroperoxide, shown in the following mechanism scheme.

$$M^{(III)} + R\text{-}H \longrightarrow M^{(II)} + R{\cdot}H^{+} \quad (1\text{-}10)$$

$$R{\cdot}H^{+} + B \longrightarrow R{\cdot} + BH^{+} \quad (1\text{-}11)$$

(B = substrate, solvent, or base)

$$R{\cdot} + O_2 \longrightarrow RO_2{\cdot} \quad (1\text{-}12)$$

$$RO_2{\cdot} + R\text{-}H \longrightarrow RO_2H + R{\cdot} \quad (1\text{-}13)$$

This scheme is similar to the one shown in Figure 1-1, but the transition metal center in this case acts as the initiator. The second step varies and may involve simple Haber-Weiss decomposition (Class IV a). Nucleophilic attack of an organic substrate on the metal-bound peroxo complex constitutes the (Class IV b) mechanism.

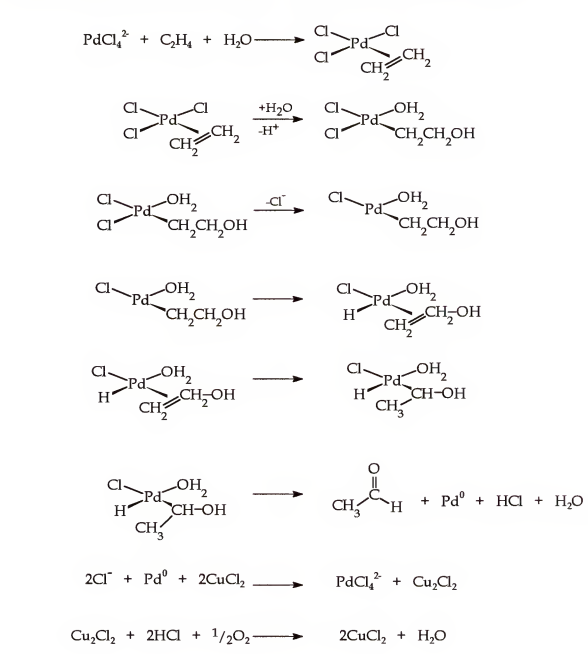

Figure 1-6.[68] Wacker process for oxidizing ethylene to acetaldehyde.

Class V reactions involve metal-centered oxidizing agents. A transition metal complex in a high oxidation state oxidizes an organic substrate. The reduced complex is re-oxidized by molecular oxygen or peroxide to regenerate the catalyst. The Wacker process for the production of acetaldehyde is a well known example of this type of reaction and is shown in Figure 1-6.[68]

The work presented in this dissertation is divided into two major sections. The first section discusses zeolite-encapsulated transition metal complexes that employ shape selectivity to control reaction pathways of saturated hydrocarbon oxidations. The goal was to find effective heterogeneous catalysts for the conversion of cyclohexane and cyclohexane derivatives to adipic acid. Adipic acid is an industrially important compound and present industrial production have environmental concerns. Finding an alternative system in synthesizing adipic acid to address these environmental concerns was the major motive for this research. This research accounts for the first reported oxidation system that utilizes an alkylhydroperoxide as the oxidant in adipic acid synthesis.

The second section discusses the development and utilization of chiral transition metal complexes that were used in stereoselective epoxidations of nonfunctionalized olefins. The goal in this case was to find effective enantioselective catalysts that are easily synthesized. The use of Schiff base complexes derived from amino acids is a novel approach to enantioselective epoxidations. The production of chiral molecules has great significance in pharmaceutical applications and natural products synthesis.

CHAPTER 2
CONTROL OF REACTION PATHWAYS WITH A ZEOLITE: A ONE STEP SYNTHESIS OF ADIPIC ACID

Introduction

Introduction to Zeolites

Zeolites are well defined, crystalline structures that are composed of aluminum and silicon and are known as aluminosilicates. Silica and alumina tetrahedra are linked to each other by sharing oxygen atoms and classifies them as part of the tectosilicate family.[69] Zeolites have infinite networks of open channels and pores, and the nature of their structure allows for many interesting applications in chemistry.

The term zeolite is derived from the Greek words zein, which means to boil, and lithos, which means stone. They were first discovered and named in 1756 by Baron Cronstedt.[70] He observed that the aluminosilicate, stilbite, appeared to boil when heated in a flame, which was attributed to water loss. Significant developments in zeolite chemistry occurred in the following decades. In 1858, reversible ion exchange was discovered, where existing framework cations are exchanged by introducting different cations.[71] Many scientists searched for methods to prepare synthetic forms of zeolites. The first claim of this was the synthesis of levynite in 1862,.[72] Interest in the physical properties of

zeolites, such as ion exchange, selectivity as molecular sieves, and shape selectivity led the development of zeolite chemistry. Zeolites are generally known to be useful in acid catalysis because of their inherent acidity and for their ability to bind transition metal ions.

There are nearly forty different naturally occuring zeolites.[73-76] Only a few zeolites used in catalysis are found in great abundance, and even fewer are used in industrial applications. There are more than one hundred thirty different zeolite structures known, which include natural and synthetic zeolites, and each have pore openings that range from less than 3Å to over 13Å.[77-79]

There have been many classification schemes devised for zeolites because of the large number of complex structures. Since they are composed of well defined units, zeolites may be classified by the symmetry of their unit cells, but this method has complications.[80] A more effective way to classify zeolites is by pore size. This is done by grouping zeolites by the number of tetrahedral atoms, such as Si or Al, that define the pore opening. Oxygen atoms are not inculded in determining the number of tetrahedral atoms. There are three different size pore openings known in zeolite structures.[81] The 8-membered ring systems are referred to as the small ring openings, the 10-membered ring systems as the medium ring openings, and the 12-membered ring systems as the large ring openings. A representative list of known zeolites is shown in Table 2-1.[71,79] There have been recent reports of zeolites that contain ring systems of 20-

Table 2-1.[71,79] Pore Structure of Zeolites.

Zeolite Name	Type Code	Pore System	Pore Dimensions (Å)
Bikitaite	BIK	8	3.2 x 4.9
Brewsterite	BRE	8	2.3 x 5.0
Chabasite	CHA	8	3.6 x 3.7
Dachiardite	DAC	10	3.7 x 6.7
		8	3.6 x 4.8
TMA-E(AB)	EAB	8	3.7 x 4.8
Epistilbite	EPI	10	3.2 x 5.3
		8	3.7 x 4.4
Erionite	ERI	8	3.6 x 5.2
Faujasite(X,Y)	FAU	12	7.4
Ferrierite	FER	10	4.3 x 5.5
		8	3.4 x 4.8
Gmelinite	GME	12	7.0
		8	3.6 x 3.9
Heulandite	HEU	10	4.0 x 5.5
		8	4.4 x 7.2
ZK-5	KFI	8	3.9
Linde Type A	LTA	8	3.9
Linde Type L	LTL	12	7.1
Mazzite	MAZ	12	7.4
ZSM-11	MEL	10	5.1 x 5.5
ZSM-5	MFI	10	5.4 x 5.6
			5.1 x 5.5
Mordenite	MOR	12	6.7 x 7.0
		8	2.9 x 5.7
Offretite	OFF	12	6.4
		8	3.6 x 5.2
Rho	RHO	8	3.9 x 5.1
Stilbite	STI	10	4.1 x 6.2
		8	2.7 x 5.7

membered rings.[77] Within each group, there is considerable variation in the opening, both in size and ellipticity. The channel systems in zeolites also vary from one-dimensional, to two dimensional or three dimensional with multidimensional channels often intersecting each other.[82] These interconnecting channels may be the same size, different sizes, straight, or bent. The connectivity of the channel system has significant ramifications in diffusion and aging characteristics. For example, zeolites with one-dimensional channels are more susceptible to deactivation than those with three-dimensional pore systems because of their increased likelihood of pore blocking.

The 8-membered ring systems vary from circular to puckered to elliptical. The dimensions of the pore opening also vary. Members of these systems sorb straight chain molecules, such as n-alkanes and olefins. Due to constraints of the pore openings, branched alkanes are less likely to be sorbed. These pore systems also contain interconnecting supercages, which are much larger in size than the connecting pores.[83] These supercages are often blamed for the deactivation of acid catalysts, because they trap bulky molecules that result in coke deposits.[84-86] The first zeolite in this class applied to a commercial molecular shape selective catalytic process was erionite, which was used in the Selectoforming process.[84]

The 10-membered ring systems are known as the medium pore zeolites. They are very popular in shape selective catalysis since they can sorb straight chain molecules and also discriminate among branched and cyclic molecules. The shapes and sizes of these zeolites also vary, as in the 8-membered ring

systems. They range from circular to elliptical to odd shapes, such as tear drops.[85] Among all the zeolites in this class, only ZSM-5 and ZSM-11 have bidirectional intersecting channels. All others have non-intersecting, unidirectional channels. Unlike other zeolites, they have uniform pore dimensions and no supercages. The absence of supercages and their high silica to alumina ratio are believed to contribute to their unusually low coke forming tendencies when used as acid catalysts. It sterically difficult to form the large hydrocarbons responsible for coking and irreversible deactivation. Since these catalysts age more slowly, they are very successful in industrial applications.

The 12-membered ring systems include all large pore zeolites. They are generally composed of a composite of different building blocks and contain supercages and other smaller size cages. The best known example of this zeolite class is faujasite. Some zeolites may contain dual-pore systems, where the zeolites have interconnecting channels of either 12 and 8-membered pore openings or 10 and 8-membered ring pore openings. Examples of these are dachiarite, and ferrierite, mordenite, and stilbite.[87,88]

Zeolite Y - A Synthetic Faujasite

The research described in this dissertation involves the use of a synthetic faujasite called zeolite Y. The structure is shown in Figure 2-1. It is composed of a basic unit, described as truncated cubo-octahedra, called a sodalite cage.[89] These sodalite cages are connected by its hexagonal faces to form an infinite

framework that contains different size cavities. The smallest cavity lies within the hexagonal prisms that join the sodalite cages, and have a pore opening of 2.2Å that leads to a 2.4Å cavity. The sodalite units also have 2.2Å pore openings, but their cavity is 6.6Å wide. Collectively, the sodalite units link together to form a large cavity known as a supercage, which have a 7.4Å opening and a diameter of 13Å. The relative sizes of these cavities and pore sizes are shown in Figure 2-2. Only small molecules such as NH_3 and H_2O may enter the small cavities, but the larger supercages can hold larger molecules. The alumina tetrahedra in the framework provide an anionic site and the charge is countered by the presence of a cation, such as sodium, hydrogen, or ammonium. Cation sites are located in each of the three cavities, and occupancy by various cations has been studied.[90] The cations occupy specific sites in the zeolite, but they are constantly moving from site to site.[89] This implies that an ion may be in an inaccessible site in one instance, but may become accessible after migrating to the supercage. Over time, all the cations become accessible, which is important in studies of coordination compounds that are formed within zeolites.

Transition metals may be ion exchanged into zeolites. This is important in catalysis since many transition metals and their complexes are known to be active catalysts. Formation of known homogeneous catalytic transition metal complexes inside zeolites may be thought of as the process of "heterogenizing" a homogeneous catalyst. This gives inherent advantages and disadvantages.

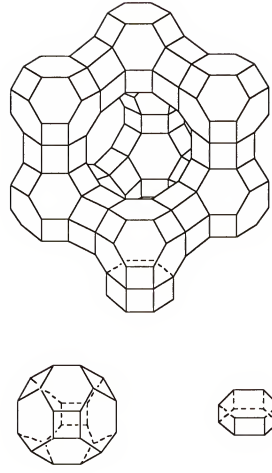

Figure 2-1. Structure of faujasite (top), a sodalite unit (bottom left), and a hexagonal prism (bottom right).

Encapsulating a complex inside a zeolite combines both homogeneous and heterogeneous qualities in one catalytic system. Activity of the encapsulated catalyst will be similar to its homogeneous counterpart. Since the catalyst is trapped inside the zeolite framework, easy recovery of the catalyst and its separation from reaction products are possible. Finally, the constraints of the zeolite framework prevent degradation and deactivation of the catalyst. The formation of μ-oxo dimers tends to deactivate oxidation catalysts, but since the limited space available in zeolite cages is unable to accommodate the formation of these dimers, catalyst life improves.

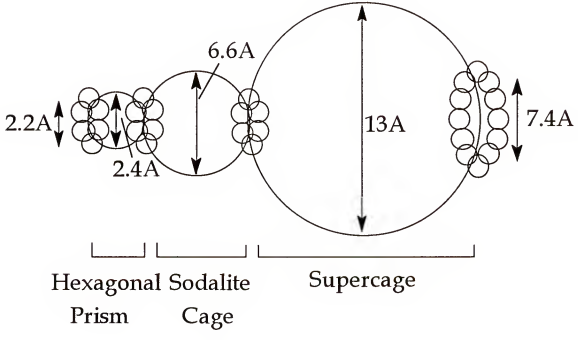

Figure 2-2.[89] Relative sizes of cavities and pore openings in zeolite Y.

There are distinct disadvantages to the use of these encapsulated materials as catalysts Since the pore sizes are small in zeolites, there is likelihood of the pores becoming blocked by reactants, reaction products and solvent molecules. Pore blocking may cause deactivation of these catalysts since reactant molecules cannot diffuse through the zeolite framework to access active sites and reaction products cannot diffuse out of the zeolite. Slower reaction times are also a factor when encapsulating a transition metal catalyst inside a zeolite. The major contributor to slower reaction times is the diffusion process. Diffusion effects on rate and selectivity occur when the rate of catalytic transformation is greater than the rate at which reactant molecules reach or product molecules escape from active sites inside the zeolite. There have been extensive studies on the determination of diffusion coefficients in zeolites.[91,92]

Shape Selectivity

One of the major benefits of employing zeolite-encapsulated transition metal catalysts is shape selectivity. Structural constraints imposed by the zeolite framework impart selectivity of molecules accessing and escaping from active sites within the zeolite. Molecular shape selectivity is imposed when the dimensions of reactant and product molecules approach those of the zeolite pores. This phenomenon has been well studied.[93,94] With shape selectivity, catalytic chemical transformations can be directed along a very specific and desired path. Many synthetic catalytic systems are class selective. For example,

a catalyst may function only as a good hydrogenation catalyst that will hydrogenate double bonds of a reactant molecule without regard of the position of the double bond. Utilizing shape selectivity via zeolite-encapsulated catalysts may give structural selectivity, including position of the reactive group, structural shape, size and symmetry.[69]

There are various modes of selectivity that may be imposed by a catalytic system of this type. Reactant selectivity was shown in the catalytic dehydration of n-butanol using Linde 5A zeolite.[95] This process occurs without reacting the more branched molecule, isobutanol. When a larger pore zeolite is used, such as zeolite X, no discrimination is observed, and both molecules are dehydrated.[95] Another form of selectivity is product selectivity. This was shown in the selective hydrogenation of a mixture of ethylene and propylene using a platinum-sodium-mordenite catalyst.[96] The reactants ethylene and propylene, and the product ethane have access into and out of the zeolite structure, but the product propane is unable to exit the zeolite.[97] Shape selectivity may also be controlled by modifiying the surface of the zeolite. Chemisorption of inorganic and organometallic complexes have been done to adjust the size of pore entrances, which were used in gas separation and gas encapsulation applications.[98]

Zeolite-Encapsulated Transition Metal Complexes

Zeolites may be thought of as a medium for carrying out coordination chemistry. The ability to ion exchange transition metals into zeolites allows for the formation of transition metal complexes when ligands are also introduced into the zeolite. Characteristics of solvent, solid state, and surface chemistry are incorporated into one system where the zeolite can function as an anion, solid, and a medium to carry out chemical reactions.[89] There have been numerous accounts of synthesizing transition metal complexes inside zeolites. The use of faujasites is desirable because of its large cavities and large pores that allow reactant molecules to enter the zeolite. Examples include transition metal complexes with ethylenediamine, bipyridine, cyanide, and amino acids.[99-109] Some of these complexes are known to reversibly bind oxygen in their homogeneous states, but disadvantages include irreversible dimerization that deactivates them as potential oxygen donors. One function of encapsulating these complexes inside zeolites is for preventing dimer formation by using the constraints of the zeolite cavities.

There are accounts of zeolite systems where oxygen adducts were formed.[100,101,106,108] Ship-in-the-bottle complexes are also known, where transition metal complexes that are too large to pass through zeolite pores are assembled within the zeolite cavities. This is accomplished by ion exchanging the transition metal into the zeolite, and then introducing the ligand into the zeolite so it may form a complex with the transition metal. The resulting complex has dimensions

that are larger than the pore openings, and it is be unable to leave the zeolite framework. Some limitations are evident in this process. First, the ligands must be small enough to enter the zeolite pores. If the dimensions of the ligand approach those of the pore opening, it is necessary for the ligand to be flexible enough to conform into a shape that is able to pass through the pore opening. Another method of introducing the ligand into the zeolite is by a method called template synthesis. After ion exchanging the metal into the zeolite, the ligand is built around the metal center. Examples of ship-in-the-bottle complexes include transition metal complexes with salen [N.N'-ethylenebis(salicylideneaminato)] and porphyrins.[110-118] The latter systems are models that mimic the mono-oxygenase cytochrome P450 and oxidations of saturated hydrocarbons and olefins have also been investigated. Each oxidation study concluded that encapsulating the transition metal complex inside the zeolite framework increased catalyst lifetime by preventing degradation pathways such as metal-oxo dimerization.[110,112-118] However, it was not shown how shape selectivity was employed in these oxidations.

Although the use of zeolites in oxidation chemistry has been limited, it is a growing field of study. Much of the focus is in mimicking natural mono-oxygenase enzymes with the type of porphyrin and salen systems described above. Recently, there have been new systems developed for shape selective oxidations using zeolites that have transition metal ions incorporated into the framework of the zeolite. The most well known system is the titanosilicate, TS-1.

This system has been used in a variety of oxidation reactions, such as alkane oxidation and olefin epoxidation.[110-123]

Adipic Acid

Adipic acid is a linear 6-carbon molecule containing two carboxylic acid groups. It is an industrially important compound that is the major precursor for the production of nylon 6,6, which involves the condensation and polymerization of adipic acid with hexamethylene diamine. Adipic acid is also used in the production of hexamethlyene diamine. It is among the top 50 synthetic chemicals produced in the United States each year.[124,125]

The production of adipic acid involves a two step process.[39,124,127-131] The DuPont process, shown in Figure 2-3, is one current technology employed in industry.[129-131] In this process, cyclohexane is autoxidized to cyclohexylhydroperoxide (CHP) under 10 atmospheres of oxygen at 165°C and is subsequently decomposed to cyclohexanol and cyclohexanone in the presence of cobalt octanoate catalyst. Nitric acid is used as the oxidant in the presence of cupric nitrate and ammonium vanadate to oxidize the alcohol and ketone mixture to adipic acid in high yields. This oxidation with nitric acid has been studied extensively, and the chemistry is very complicated. Copper nitrate and ammonium vanadate facilitate the production of nitrous acid, which enhances

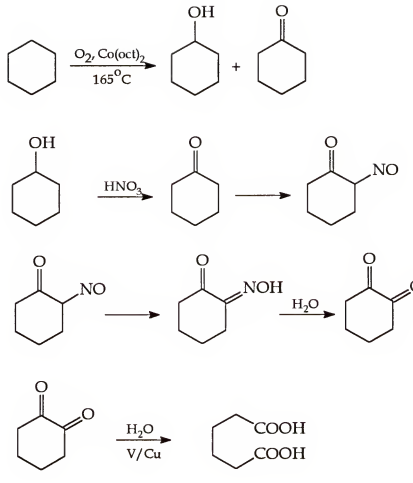

Figure 2-3.[127] DuPont Process for the conversion of cyclohexane to adipic acid.

the initiation of the reaction.[39,126] Copper nitrate also helps suppress side reactions.[126] Both catalysts are necessary to achieve high yields of 92%, which is contrasted by a 20 percent decrease when ammonium vanadate is used alone.[126] Unfortunately, the second step in the DuPont process produces one mole of N_2O per mole of adipic acid made.[125] With N_2O emissions contributing to global warming and ozone depletion, there is a worldwide agreement in the adipic acid industry to reduce these emissions within the next few years.[125]

There are various ways to deal with the N_2O problem. One is to decompose N_2O into N_2 and O_2 before it is emitted into the atmosphere.[132] A "green" chemistry solution would replace nitric acid as the oxidant. Since alkylhydroperoxides are potent oxidizing agents, it seems practical to investigate the feasibility of using CHP to catalytically oxidize cyclohexanol and cyclohexanone to adipic acid. This oxidant is generated in the first step of the present industrial process and would be utilized instead of being wasted by decomposition. The result could be a one step oxidation of cyclohexane to adipic acid. When CHP acts as an oxidant, the products are cyclohexanol and cyclohexanone. Four equivalents of CHP are required to oxidize the ketone to adipic acid and five equivalents are required per mole of alcohol. If O_2 only oxidizes cyclohexane to CHP, the four moles of CHP required by stoichiometry for adipic acid formation would generate four moles of cyclohexanone plus cyclohexanol. A 25% percent maximum yield results with the major products being cyclohexanone and cyclohexanol, in effect saving 25% of the oxidizing

equivalents needed to convert all the CHP to adipic acid. The ideal solution is to provide the additional 75% of the oxidation equivalents needed for complete conversion to adipic using the "green" oxidant, air. Reports of a one step oxidation of cyclohexane to adipic acid in acetic acid solvent have appeared with yields of up to 75% adipic acid.[133-137]

This chapter investigates some of the fundamental catalytic chemistry that would be relevant to a one step adipic acid synthesis. We will show that O_2 can provide needed oxidative equivalents in a catalytic oxidation of the cyclohexanone and cyclohexanol by intercepting radicals generated in the catalyzed CHP oxidation. In the process, a novel application of zeolites was discovered where the diffusion of reactants into the pores to access the catalyst regulates the chemistry that occurs. The zeolite is in effect performing as a molecular V-chip that screens out an undesirable reaction. The concept is a general one that is illustrated in this example by selecting the productive reaction involving oxidized catalyst reacting with substrate instead of the non-productive reaction of oxidized catalyst with CHP leading to catalyzed decomposition.

Experimental

Reagents and Equipment

All reagents were reagent grade or better. All halide salts, sodium hydroxide, glacial acetic acid, ACS reagent grade 2-propanol and sodium thiosulfate were purchased from Fisher Scientific and used as received. Neocuproine (1,9-dimethyl-1,10-phenanthroline or dmp) was purchased from Eastman Fine Chemicals and was used as received. Cyclohexanol and cyclohexanone was purchased from Mallinckrodt, dried over 5A molecular sieves and used without further purification. ACS reagent grade cyclohexane from Fisher Scientific was distilled over P_2O_5 and stored over 5A molecular sieves before use. Benzene, decane and 90% TBHP, in 10% H_2O, were obtained from Aldrich and used as received. Zeolite Na-Y was obtained from Aldrich, lot number 06708LF, and was pre-treated by ion exchanging the zeolite with a 0.85M solution of NaCl for 24 hours followed by washing with deionized water until the filtrate gave a negative chloride test with $AgNO_3$. Cyclohexylhydroperoxide, CHP, as a 4.10M solution was obtained from Monsanto Chemical Company and its titre was determined before use.

Volatile products and reactants of all oxidation reactions were monitored by gas chromatography. A Hewlett Packard 5890, equipped with a Hewlett Packard 50+ column (crosslinked 50% Phenyl Methyl - 30m x 0.53mm x 1.0 um film thickness), helium carrier gas, flame ionization detector, and a Hewlett

Packard 3396 Series II integrator were used. Substrates and products were identified using known standards. Calibration curves were used to relate peak areas to the number of moles of products and reactants. 0.50 mL of benzene or 0.10 mL decane were added to each reaction as an internal standard.

Iodometric and Acid/Base Titrations

Iodometric titrations were used to determine organic peroxide concentration. The procedure involves refluxing a mixture of 25 mL of 2-propanol, 1 mL of glacial acetic acid, 0.1 mL of sample and 10 mL of a saturated solution of NaI in 2-propanol for one minute, and titrating with a standardized solution of sodium thiosulfate. Peroxide concentration is calculated from the reaction stoichiometry. Peroxide efficiency is calculated with Equation 2-1:

$$\text{Peroxide Efficiency} = \frac{(\text{mol. of adipic acid})(\#\text{ of oxidative equiv.})}{(\text{moles of peroxide decreased})} \qquad (2\text{-}1)$$

Diprotic acids can not be identified by GC due to low volatility of these compounds. In the most promising reactions, samples were submitted to Monsanto Chemical Company in Pensacola, FL for GC/MS analyses by a proprietary method. ^{1}H NMR spectroscopy was carried out on the precipitated colorless solid.

The yields presented in this chapter are total acid yields unless stated otherwise. ^{1}H NMR resonances of other diprotic acids such as succinic acid and glutamic acid are different from adipic acid and were not observed in most samples. Thus the total acid content predominantly measures adipic acid yield in all reactions.

Acid base titrations of the samples using a standardized solution of NaOH were done to determine total acid content. The procedure is as follows: 1.00 mL of sample was placed in an Erlenmeyer flask with 40 mL of deionized water. The solution was titrated to a pH of 8.3, which corresponds to the pH of sodium adipate in 40 mL of water, with a standardized solution of NaOH, and the pH was monitored by the use of a Fisher Accumet pH meter (Model 630) equipped with a combination electrode. The calculations for total acid yield were made assuming that all acid products are diprotic. Acid yields were based on the limiting reagent used for the oxidation reaction.

Preparation of Transition Metal Exchanged Zeolites

Na-Y was pre-treated by stirring 40g of Na-Y and 10g of NaCl in 400 mL of distilled water to ensure that all the cation sites were occupied by Na ions. The suspension was stirred for 24 hours and filtered. The sample was dried at 110^{0}C for 24 hours under vacuum.

M-Y (M=Co^{2+}, Mn^{2+}, and Fe^{3+}) samples containing $5x10^{-4}$ moles of transition metal cation per gram of zeolite were prepared by the ion exchange of

Na-Y with the appropriate transition metal salt. 0.02 moles of a transition metal salt ($CoCl_2 6H_2O$, $Mn(OAc)_2 4H_2O$, and $FeCl_3$) was ion exchanged in to 40 grams of pretreated Na-Y by stirring the dissolved metal salt with the zeolite in 600 mL of distilled water for 48 hours at 70°C. For the Mn^{2+} exchange, the slurry was stirred at room temperature instead of 70°C. The sample was filtered and successively washed with water until all the chloride ions were completely washed away as tested by adding 0.1M $AgNO_3$ to the filtrate. The resulting M-Y was dried in a vacuum oven at 110°C for 24 hours. The dried solid contains $5x10^{-4}$ moles of M^{n+} per gram of zeolite Y as confirmed by atomic absorption.

Preparation of $Co(dmp)_2Cl_2$, Co(dmp)-Y, Ru(dmp)-Y and VO(dmp)-Y

$Co(dmp)_2Cl_2$ was prepared according to a literature procedure in which 2,9-dimethyl-1,10-phenanthroline was added to an ethanolic solution of $CoCl_2$ in a 2:1 ligand to metal ratio.[138] 1 mL of concentrated HCl and 1 mL 30% H_2O_2 was added, and the solution was refluxed for 24 hours. The blue precipitate that was formed was filtered, washed with acetone and dried under vacuum at room temperature. Analysis: Found for $Co(dmp)_2Cl_2$: C, 61.25%; H, 4.51%; and N, 9.67%. UV/Vis: peak maxima at 658 nm and 580 nm. Calculated for $Co(dmp)_2Cl_2$: C, 61.55%; H, 4.43%; and N, 10.25%.

Co(dmp)Y was prepared by adding 5.0 grams of Co-Y to 2.31 grams of 2,9-dimethyl-1,10-phenanthroline dissolved in 475 mL absolute ethanol. The

suspension was stirred 24 hours and filtered. The resulting blue sample was then washed with absolute ethanol, Soxhlet extracted with ethanol, and vacuum dried for 72 hours at 110°C.

Analysis: Found for Co(dmp)-Y: A.A. analysis, A=0.309, SD = 0.0020, RSD = 0.6466, ppm Co^{2+} = 57.71, 4.85 x 10^{-4} mol Co^{2+}/gram zeolite. UV/Vis: peak maxima at 570nm and 635 nm.

VO(dmp)-Y was prepared by initially preparing V(O)-Y. Stirring 0.02 mmols of vanadyl sulfate 40g of pretreated Na-Y in water heated to 70°C gave V(O)-Y. The sample was filtered, washed with deionized water, and dried under vacuum at 110°C for 72 hours. 5.0g of V(O)-Y was added to an ethanolic solution containing 2.31g of dmp and 400 mL absolute ethanol. The slurry was stirred for 48 hours at room temperature. Filtration of the slurry yielded a pale green solid, which was then washed with absolute ethanol, Soxhlet extracted with ethanol, and dried under vacuum for 72 hours at 110°C.

Ru(dmp)-Y was prepared in two steps. $Ru^{III}(NH_3)_6$-Y was prepared by a modified procedure used by Marazewski and co-workers.[139] 10g of zeolite Y and 0.02 moles of $Ru(NH_3)_6Cl_3$ were stirred in 400 mL of deionized water for 24 hours, and the resulting grey solid was filtered and washed with deionized water until a negative chloride test resulted. The $Ru^{III}(NH_3)_6$-Y was then stirred in a solution containing 0.463g of dmp and 200 mL of absolute ethanol for 24 hours. The ethanol was then removed under vacuum. The solid was purged with nitrogen for 30 minutes and then evacuated for another 24 hours at 180°C.

After cooling to room temperature, the orange solid was washed with absolute ethanol, and dried under vacuum at 110°C.

Oxidation of Substrates Using Various Alkylhydroperoxides

The substrates oxidized were cyclohexane, cyclohexanol and cyclohexanone, which were either reacted individually or as mixtures. The alkylhydroperoxides used in these studies were tertiary butylhydroperoxide, TBHP, and CHP. In a typical stoichiometric reaction, substrate and oxidant were placed in a 250 mL pressure bottle along with the appropriate amount of transition metal exchanged zeolite catalyst. The oxidative equivalents varied, depending on the substrates used. For complete conversion to adipic acid, cyclohexane, cyclohexanol, and cyclohexanone require, respectively, 6, 5, and 4 oxidative equivalents. Reactions were run using substrate to oxidant ratios of 6 to 1 for the oxidation of cyclohexane, 5 to 1 for cyclohexanol, and 4 to 1 for cyclohexanone. The bottle was stoppered with a pressure head and the reactor was placed in an oil bath set at the desired temperature. Samples were taken periodically and analyzed by GC, iodometric titration and acid/base titration. Dibasic acids were recovered as a precipitate in most reactions, and were analyzed by ^{1}H NMR. For reactions involving a 1:1 substrate to oxidant ratio, 185 mmol of cyclohexane and 185 mmol TBHP were used and reacted in a batch reactor as described above. The limiting reagent in the 1 to 1 substrate to oxidant ratio reactions is TBHP. Analysis: Found for adipic acid: ^{1}H NMR (DMSO): δ 2.45 (t, J = 6.0 Hz, 4H),

δ 2.72 (t, J = 6.0 Hz, 4H), δ10.8 (s, 2H). ^{13}C NMR (DMSO): δ 24.36, δ 33.75, δ 174.9. IR: 3400-2700 cm^{-1}, br; 1695 cm^{-1}, s; 1279 cm^{-1}, s; 1194 cm^{-1}, m; 925 cm^{-1}, m.

Cyclohexanone Oxidation by THBP and Oxygen

In a 250 mL pressure bottle, 28.9 mmol of cyclohexanone were added along with 10.4 mmol TBHP and 0.25 mole % Codmp-Y. Enough TBHP was added to theoretically convert 9.0% of the substrate to adipic acid. The bottle was stoppered with a pressure head and pressurized to 50 psig oxygen. The reaction was periodically monitored by GC analysis, iodometric titration, and acid/base titration.

Oxidation of Cyclohexane With Air Using CHP as the Initiator

In a titanium autoclave (Parr Instruments), 17.0 mL of cyclohexane, 3.0 mL CHP (12.296 mmol), and 0.500 mL decane were combined with approximately 2.7 grams of Codmp-Y. The autoclave was pressurized to 700 psig with air, heated to 100°C, and run for 24 hours. In some cases, cyclohexanol and cyclohexanone were added and their ratio with respect to cyclohexane varied. Samples were taken periodically and analyzed by GC, iodometry, and acid/base titration.

Results and Discussion

Catalyzed Oxidations of Cyclohexanone, Cyclohexanol and Cyclohexane with TBHP

There are very few examples of the use of zeolite catalysts in adipic acid synthesis. In one report, a zeolite Y-occluded manganese diimine complex catalyzed the oxidation of cyclohexene by H_2O_2.[140] Iron-phthalocyanine encapsulated in zeolite Y is reported[141] as a catalyst for the oxidation of cyclohexane and cyclohexanone with tertiary butylhydroperoxide, TBHP. There are other examples of cyclohexane oxidation using transition metals and complexes encapsulated in zeolite Y and titanosilicates, but adipic acid was not detected in those cases.[114-121]

The initial study focused on the homogeneous oxidation of cyclohexanone, which was carried out with TBHP using the soluble $Co(dmp)Cl_2$ complex at 80°C. Extensive decomposition of TBHP occurs, giving 12.1% conversion to diprotic acids with a peroxide efficiency of 22.0% after 45 minutes. In the Haber Weiss decomposition, a TBHP molecule oxidizes Co(II) to Co(III) and the subsequent reaction of Co(III) with another TBHP will reduce the Co(III) back to Co(II), completing the cycle for TBHP decomposition.[41] Slowing this decomposition is necessary for this system to be effective in producing adipic acid. An effective method of slowing down peroxide decomposition is encapsulating the $Co(dmp)_2Cl_2$ inside zeolite Y. The zeolite limits the access of

TBHP to the active metal center, thereby slowing Haber-Weiss decomposition. To access Codmp in zeolite Y, TBHP must diffuse through the pores of the zeolite. We propose that the zeolite slows the decomposition reaction, enabling the reaction of Co(III) with the substrate to occur by hindering the TBHP access to the metal center. This proposal constitutes a novel application of shape selectivity in which the cobalt initiates the propagation reactions with the substrate to avoid the Co(III) reduction required for the Haber-Weiss decomposition.

The following studies focused on a material prepared by reacting Co(II) exchanged zeolite Y with 1,10-dimethyl-2,9-phenanthroline. The similarity of the electronic spectrum of this material and that of $Co(dmp)_2Cl_2$ suggests coordination of this ligand to Co(II) in the zeolite.

The first substrates selected for oxidation were cyclohexanol and cyclohexanone since these compounds are the expected intermediates in a one step adipic acid synthesis. TBHP was chosen initially to determine the feasibility of the cyclohexanone and cyclohexanol oxidation to adipic acid because it has high thermal stability in organic solutions, it is soluble in most hydrocarbon solutions, and the co-product is tertiary butylalcohol, which is stable to further oxidation. Reactions 1 and 2 in Table 2-2 show the results of the oxidation of an cyclohexanol/cyclohexanone mixture and the neat cyclohexanone by TBHP using Codmp-Y at 50°C. At these conditions, oxidation of cyclohexane proceeds

Table 2-2. Oxidation of cyclohexanol and cyclohexanone by TBHP and metal encapsulated zeolite Y catalysts.

	substrate	catalyst	mol % metal in zeolite Y[c]	substrate :oxidant ratio	Temp (°C)	Time (hours)	Acid Yield (%)[a]
1	ol/one	CodmpY	1.0	1:1	50	172	73.8
2	one	CodmpY	1.0	1:1	50	172	60.4
3	one	CodmpY	0.50	4:1[b]	100	24	74.0

a) The catalyst loading is $5x10^{-4}$ moles of Co per gram of zeolite, and this % was calculated as the ratio of the moles of Co to the moles of substrate

b) Stoichiometric reaction between substrate and oxidant

c) Based on limiting reagent and determined by acid/base titration of the reaction sample with a standardized NaOH solution.

Reactions were monitored by GC

for 172 hours before the oxidant is completely consumed, while the cyclohexanol/cyclohexanone reaction mixture requires 104 hours. GC/MS indicated that the product of reaction 1 consisted of 95.1% adipic acid, 4.3% glutamic acid and 0.6% succinic acid. The corresponding products for reaction 2 were 95.6%, 3.8% and 0.6%. In these reactions and other reactions not analyzed by GC/MS, a precipitate was isolated, whose ^1H NMR and IR spectra correspond to adipic acid. Glutamic, succinic, and other adsorption bands were not detected, indicating that the titration for total acid corresponds to at least 95% adipic acid.

Reactions 1 and 2 in Table 2-2, which demonstrate selective oxidation to adipic acid, employed a 1:1 substrate to oxidant ratio. Since the stoichiometry to convert cyclohexanol and cyclohexanone to adipic acid require 5 and 4 oxidative equivalents respectively, all subsequent oxidations involved the use of stoichiometric amounts of oxidant.

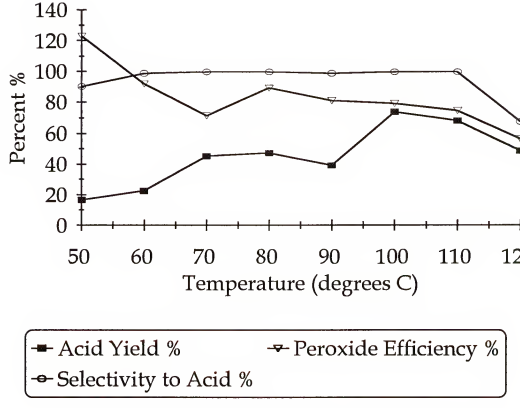

Figure 2-4. The effect of temperature on the oxidation of cyclohexanone using Codmp-Y.

The influence of temperature on the oxidation of cyclohexanone was investigated in batch pressure reactors, with the results shown in Figure 2-4. An acid yield of 58.1% was obtained after 24 hours at 100 °C. This reaction was carried out for another 24 hours, giving 83.4% acid yield with 100% peroxide efficiency. There is a gradual increase in acid yield from 50 °C to 100 °C with a decrease observed at higher temperatures. At temperatures higher than 100 °C the drop in peroxide efficiencies, which measures the relative importance of the adipic acid reaction compared to metal catalyzed decomposition, suggests that the Haber Weiss decomposition pathway becomes predominant, which leads to a drop in acid yield.

At 50°C, a peroxide efficiency of 123 % was observed. This result suggests utilization of molecular oxygen in the air above the liquid in the reactor for substrate oxidation. In the absence of TBHP, no reaction was observed between cyclohexanone and air with the catalyst indicating that TBHP initiates the oxidation and oxygen is involved in subsequent steps of the oxidation reaction sequence. The role of molecular oxygen will be discussed in more detail later in this chapter.

Easy separation of these heterogeneous catalysts from the reaction products allows for recovery and reuse. Codmp-Y was collected from all previous cyclohexanone oxidations, and was washed with absolute ethanol, filtered, and dried at 100 °C. The recovered Codmp-Y was reused in the cyclohexanone oxidation at 100°C giving 52.3% acid conversion, 77.4% peroxide

efficiency and 100% selectivity. These results are nearly identical to those of the freshly prepared catalyst indicating that no catalyst degradation or permanent pore blockage occurs.

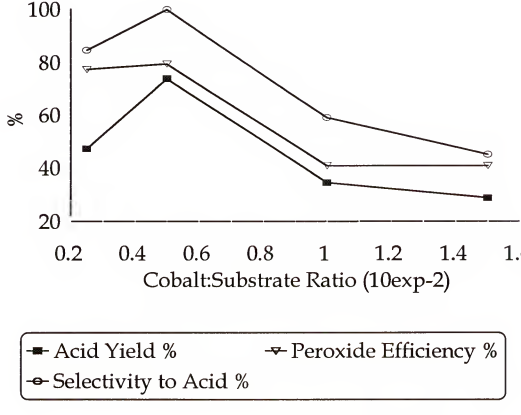

Figure 2-5. Effect of catalyst amount on cyclohexanone oxidation. Reactions were carried out at 100°C for 18 hours.

A study where the amount of the Co(dmp)-Y catalyst used was varied was carried out for the oxidation reaction at 100°C and is shown in Figure 2-5. The catalyst amount is converted to moles of cobalt per mole of cyclohexanone used. Increasing the amount of Co(dmp)-Y from 0.25 to 1.12 mole percent, 0.16g to 0.72g, shows a marked decrease in acid yield, selectivity, and peroxide efficiency. Since the probability that TBHP or substrate will react with Co(III) is independent of the amount of catalyst employed, this result implies hydroperoxide decomposition by the metal complex on the outer surface of the Co(dmp)-Y.

Oxidations Using Cyclohexylhydroperoxide

Cyclohexylhydroperoxide, CHP, was investigated for use as a potential oxidant with the Co(dmp)-Y catalyst. As explained previously, the industrial process of synthesizing adipic acid involves the production and decomposition of CHP. The ability to utilize CHP rather than simply decomposing it would be an economic advantage. When CHP functions as an oxidant, the byproducts are cyclohexanol and cyclohexanone, which are also the byproducts of CHP decomposition. The results of the oxidations using CHP are shown in Table 2-3.

Upon addition of Codmp-Y to the reaction solution, heating and effervescence indicates that the CHP is decomposed at a more rapid rate than TBHP. CHP has easier access into the zeolite pores, and should diffuse inside to interact with a Co ion faster than the more bulky THBP. This experimental

Table 2-3. Oxidations using Cyclohexylhydroperoxide[a]

Substrate	Turnovers[a]	Adipic Acid Yield[b]	Peroxide Efficiency[c]
cyclohexane	105	32.4%	39.2%
cyclohexanol/cyclohexanone	110	27.2%	39.1%

a) Turnover numbers were calculated using the equation:

$$TON = \frac{\text{moles of Adipic Acid}}{\text{(moles of Co in catalyst) x (number of cycles)}}.$$

-the number of cycles represent the number of oxidative equivalents required for each substrate.

b) Based on the percentage of the moles of substrate added to the reaction without accounting for the co-products produced by the decomposition of CHP.

c) Calculated as described in the Experimental section.

d) All reactions were run at 50°C for 24 hours using 0.25 mole % Codmp-Y.

observation is consistent with the V-chip mechanism proposed earlier and suggests that zeolite optimization could improve the utilization of CHP oxidative equivalents.

Regardless of the substrates used, the adipic acid yields were nearly identical in all reactions using CHP as the oxidant. The higher-than-expected adipic acid yield for cyclohexane may be accounted for by considering the decomposition of CHP to cyclohexanol and cyclohexanone in the initial oxidation of cyclohexane. Subsequent oxidation by Co(III) favors the newly

generated cyclohexanol and cyclohexanone in the vicinity of the catalyst. In this scenario, the system functions to convert CHP into adipic acid without the involvement of cyclohexane. Although low adipic acid yields resulted, CHP was utilized rather than simply being decomposed.

Catalyzed Oxidations With TBHP and O_2

The peroxide efficiency of 123% in Figure 2-4 suggests that oxygen may be utilized in the oxidation of cyclohexanone using Codmp-Y. Although a stoichiometric amount of oxidant was used to oxidize cyclohexanone at 50°C, peroxide efficiency was calculated to be in excess of 100%. Another source of oxidant is necessary to account for all the acid products and the only possibility is the air atmosphere above the reaction mixture. Utilizing oxygen or air instead of the more expensive hydrogen peroxide or alkylhydroperoxide oxidants is necessary for an economically viable process in large scale production.

Reactions 1 and 2 in Table 2-4 are oxidations of cyclohexanone using oxygen and only enough TBHP as the initiator to convert 10% of the total substrate. Argon was used in the control experiment. The results show that molecular oxygen provides oxidation equivalents to the alkylhydroperoxide-initiated oxidation of cyclohexanone, as observed by a three fold decrease in the acid yield in the absence of oxygen. In the absence of TBHP, little acid is formed as observed in reaction 3 of Table 2-4.

Table 2-4. Oxidation of cyclohexanone using molecular oxygen.[a,b]

	Substrate	Gas[a]	Acid Yield (%)[b]	Temp (°C)	Initiator[c]
1	cyclohexanone	O_2	10.2	50	TBHP
2	cyclohexanone	Ar	3.4	50	TBHP
3	cyclohexanone	O_2	0.2	50	none

a) The batch reactor was pressurized with 50 psi of gas at room temperature.

b) Calculated as the percentage of the moles of cyclohexanone

c) Enough initiator was added to theoretically convert 9.0% of the substrate to adipic acid

Reactions were run for 24 hours using 0.25 mol% CodmpY

TBHP initiates the oxidation reaction by oxidizing Co(II) in zeolite Y to Co(III)OH. The Co(III)OH, which is not generated with O_2, is needed to abstract the α-hydrogen atom of cyclohexanol or cyclohexanone and is reduced by these substrates, and prevents hydroperoxide decomposition. Subsequent reaction of the cyclohexanone and cyclohexanol radicals with oxygen leads to the formation of adipic acid. The tertiary butoxy radical may also be involved in a hydrogen atom abstraction reaction with cyclohexanone or cyclohexanol to form t-butanol.

Oxidation of cyclohexane with TBHP using Codmp-Y shows a one step oxidation that forms adipic acid, as shown in Table 2-5. In these cases, it is proposed that TBHP oxidizes Co(II) to Co(III)OH, and the interaction of cyclohexane with Co(III)OH results in hydrogen abstraction from the substrate. The cyclohexyl radical undergoes an oxidation reaction via interaction with

TBHP to initially produce cyclohexanone and cyclohexanol. Air is present in the reactor, so O_2 and TBHP are probably involved in subsequent oxidations. The desired utilization of the molecular V-chip concept in this chemistry would employ CHP. Further study of this catalyst was carried out with this oxidant.

Table 2-5 Oxidation of cyclohexane using TBHP and Co encapsulated zeolite Y

	Substrate	catalyst	mol % Co[a]	substrate:oxidant ratio	Temp (°C)	Time (hours)	Acid Yield (%)[b]
1	-ane	CoY	1.0	1:1	50	48	4.2
2	-ane	CodmpY	1.0	1:1	50	48	22.2
3	-ane	CodmpY	0.25	4:1	50	48	5.7

a) The mole % of Co is the percentage of the moles of Co in the catalyst compared to the amount of substrate used.

b) The Acid Yield is the percentage of the moles of Acid determined via acid/base titrations compared to the moles of the substrate.

Table 2-6 shows a comparison of various zeolite catalysts used in the cyclohexanone oxidation with TBHP. A comparison between the use of Co(dmp)-Y and the homogeneous $Codmp_2Cl_2$ clearly shows that the zeolite slows down the decomposition of the alkylhydroperoxide via shape selectivity. Comparison between Co(dmp)-Y and Co-Y shows that Co-Y is almost as effective as a catalyst in this reaction, giving 74% and 54% acid yield,

Table 2-6 Comparison of various catalysts used in cyclohexanone oxidation using TBHP[a]

Catalyst	Acid Yield %[c]	Peroxide Efficiency %[d]	Selectivity to Acid %[e]
none	3.3	100	100
$Codmp_2Cl_2$[b]	12.1	22.0	45.7
Na-Y	18.2	67.4	83.4
Co(dmp)-Y	74.0	79.5	100
Co-Y	54.1	88.0	64.1
Fe^{III}-Y	38.6	35.8	74.2
Ru(dmp)-Y	36.0	32.4	96.9
Mn(salen)-Y	40.7	76.4	71.6
Rh^{III}-Y	48.5	99.9	94.5
Mn-Y	34.5	95.4	41.0
VO(dmp)-Y	14.9	18.2	68.3

a) Reactions were run for 24 hours at 100°C

b) This reaction was stopped after 45 minutes since severe peroxide decomposition consumed all the peroxide

c) The Acid Yield is the percentage of the moles of Acid determined via acid/base titrations compared to the moles of the substrate.

d) The Peroxide Efficiency was calculated according the method described in the Experimental section.

e) The Selectivity to Acid is percent moles of adipic acid produced compared to the moles of substrate consumed in the reaction.

Reactions were monitored periodically by GC.

respectively. As shown in Table 2-6, none of the other metal encapsulated zeolite Y catalysts showed the activity observed with Co(dmp)-Y or Co-Y. Cobalt undergoes one electron redox changes readily which helps facilitate the radical chemistry occurring in these oxidations.

Catalyzed Oxidations With CHP and O_2 Using Co-Y

The oxidation of cyclohexane-CHP mixtures with air shows the CHP oxidative equivalents can be utilized, rather than wasting them, as is presently done in the decomposition of CHP to cyclohexanone and cyclohexanol in the two step industrial synthesis of adipic acid. Table 2-7 shows that the additional oxidative equivalents needed to convert all of the CHP to adipic acid can be provided by air using Co-Y as the catalyst. Using a higher cyclohexanone/cyclohexanol to cyclohexane ratio leads to an increase in the acid yield. The optimum mixture contains cyclohexanol, cyclohexanone and cyclohexane in a 1 : 1 : 4 ratio giving an acid yield of 6.610 mmol, with 59.44% selectivity. The increase of acid yield in this solvent mixture compared to cyclohexane may be attributed to the higher concentration of cyclohexanol and cyclohexanone. The cyclohexanol and cyclohexanone solubilize adipic acid and prevents partial plugging of the zeolite pores.

Table 2-7. Cyclohexane oxidation using 700 psig air, CHP, and Co-Y at 100°C for 24 hours.

Substrate	-one/-ol[a] : ane ratio[a]	mmol Acid[b]	decrease CHP mmol[c]	Selectivity to Acid %[d]
Cyclohexane	n/a	4.608	4.608	39.60
Cyclohexane	41:59	5.670	9.221	61.50
Cyclohexane	50:50	6.610	11.12	59.44
Cyclohexane	23:67	3.403	15.26	22.96

a) Equimolar amounts of -ol and -one were used

b) mmol Acid was determined by acid/base titrations

c) Calculated by iodometric titrations.

d) The Selectivity to Acid is percent moles of adipic acid produced compared to the moles of substrate consumed in the reaction.

Furthermore, we believe the CHP oxidizes Co(II) to Co(III)OH, which then undergoes a redox reaction with cyclohexanone and cyclohexanol in the pore. In solution, this reaction competes with Haber Weiss decomposition of CHP, wasting the oxidative equivalents. The activation of cyclohexanone or cyclohexanol by Co(III)OH occurs by hydrogen abstraction generating cyclohexanone or cyclohexanol radicals that react with molecular oxygen in air to give adipic acid. Reaction of Co(III)OH with cyclohexane is also possible, and this would generate more CHP while reaction of Co(III)OH with CHP would generate Co(II) and a $C_6H_{11}O_2\cdot$ radical. The extent to which the chain reactions occur within, or outside the zeolite is not known. The key point is that the

initiation steps of the oxidation reactions of cyclohexanone and cyclohexanol to adipic acid occur within the zeolite.

Conclusions

The one step oxidations of cyclohexane, cyclohexanol, and cyclohexanone using tertiary-butylhydroperoxide, cyclohexylhydroperoxide and oxygen were investigated. Initial studies involved the oxidations of the cyclohexanol and cyclohexanone since they are expected intermediates in a one step adipic acid synthesis. The oxidation of cyclohexanone homogeneously catalyzed by a $Co(dmp)_2Cl_2$ complex exhibited severe decomposition of TBHP, which is indicative of a Haber-Weiss pathway. It was found that encapsulating the $Co(dmp)_2$ inside zeolite Y slowed down the Haber-Weiss pathway. It is proposed that this control of reaction pathways occurs by shape selectivity, where a relatively bulky TBHP has a somewhat hindered approach to the metal center. The use of CHP as an oxidant is an attractive method of synthesizing adipic acid. CHP, which is normally decomposed in the industrial synthesis of adipic acid, was utilized as an effective oxidant in adipic acid synthesis, using the zeolite Y-encapsulated $Co(dmp)_2$. Air was utilized as an oxidant source, but requires an initiator such as TBHP or CHP. It was determined that cobalt doped zeolite Y was an effective catalyst in the oxidations using CHP and air.

CHAPTER 3
ASYMMETRIC EPOXIDATIONS USING CHIRAL SCHIFF BASE COMPLEXES

Introduction

Enantioselective Transformations

The control of stereochemical selectivity is a continuing challenge to chemists. It is a growing area where optically pure compounds are important targets for the synthesis of numerous pharmaceuticals and natural products.

A reaction of a prochiral substrate under achiral conditions may give products that are racemic, where a mixture of enantiomers are formed in a one to one ratio. Under chiral conditions, the reaction may proceed to form one enantiomer preferentially and yielding one enantiomer in excess. This is the basis of an enantioselective reaction. Non-racemic chemical products may be formed by several fundamental enantioselective strategies including nonenzymatic asymmetric induction, enzymatic asymmetric induction, nonenzymatic asymmetric resolution, and enzymatic asymmetric resolution.[142-150]

One way to achieve enantioselective induction is by the use of chiral transition metal catalysts. Besides asymmetric induction, one major advantage of employing chiral catalysts is they accelerate the progress of a reaction when

compared to the non-catalyzed counterpart. There are several requirements chiral catalysts must meet to achieve high levels of enantioselectivity. First, the transition metal complex must be catalytic, where the catalyst is involved in a reaction cycle more than once. The prochiral substrate must also be in close proximity to both the active metal center and the chiral centers on the ligands so the substrate may be directed to the active metal center in a stereochemical manner.[151] Finally, the interaction between the substrate and the catalyst may be induced by either secondary bonding interactions or nonbonding interactions.

Introduction to Epoxidation Chemistry

Epoxidation chemistry is a class of oxidation in which an oxidant reacts with a carbon-carbon double bond to form a three-membered ring containing an oxygen atom and two carbon atoms. Epoxides are naturally occurring highly strained ring compounds and are useful intermediates in the synthesis of important compounds such as polymers, pharmaceuticals, and natural products.

The classical mechanism of a non-catalytic epoxidation, as shown in Figure 1-3 a), involves the oxidation of an olefin using a peroxyacid. The distal oxygen of the peroxyacid is transferred to the olefin by a concerted pathway and forms the three membered epoxide ring and the corresponding carboxylic acid. Commonly used peracids are peroxyacetic acid and meta-chloroperoxybenzoic acid, MCPBA. MCPBA is a popular peracid because it is a solid and is easily transported and stored. Many peracids are unstable, but can be formed prior to

use by reacting a carboxylic acid with hydrogen peroxide. Non-catalytic epoxidation may also be achieved by the direct use of peroxides such as hydrogen peroxide and alkylhydroperoxides.

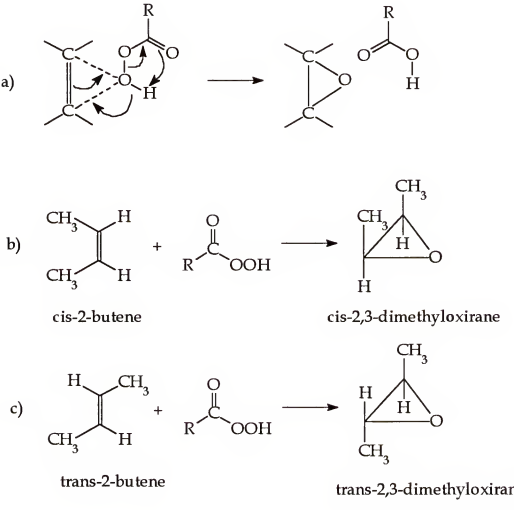

Figure 3-1. Classical epoxidation mechanism - a) The reaction between a peracid and an olefin. b) and c) Stereoselectivity in epoxidations

Epoxidation is very stereospecific and gives syn addition of an oxygen atom to a carbon-carbon double bond. Depending on the starting olefin, very specific epoxides are formed, as shown in Figure 1-3. The reaction of cis-2-butene with a peracid gives the corresponding cis-epoxide while the reaction of the trans-2-butene with a peracid gives the trans-epoxide. A complete retention of alkene stereochemistry is exhibited. The oxygen from the peracid must bond to both olefin carbons on the same face since it cannot bridge both upper and lower faces simultaneously.

It is also possible to synthesize epoxides by the Williamson ether synthesis as shown in Figure 3-2. An alkene is normally the starting material and is initially converted to a halohydrin. Abstraction of the alcohol proton by a base is followed by an intramolecular nucleophilic attack to yield the epoxide.

The most important commercial epoxide is ethylene oxide, which is produced in excess of 4 million pounds per year.[152] Ethylene oxide is commercially synthesized by the direct air oxidation of ethylene using a silver catalyst. It is used as an intermediate in the synthesis of ethylene glycol and other derivatives, including polyethylene glycol, glycol ethers, ethanolamine and surfactants.

Many studies of catalytic epoxidation have been inspired by the interest in the enzymatic cytochrome P-450 systems. Cytochrome P-450 systems are iron-containing enzymes that function as extremely effective stereoselective oxidation

systems.[153] Under appropriate conditions, cytochrome P-450 systems have been demonstrated to mediate enantioselective epoxidation of prochiral olefins.[154-157]

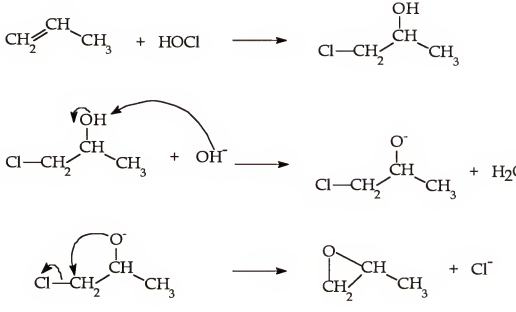

Figure 3-2. Epoxide formation via the Williamson ether synthesis

It is not the active metal center that facilitates asymmetric induction, but it is the ligand environment bound to the active metal center. In cytochrome P-450 systems, the active site is an iron porphyrin bound to a cysteine thiolate group of the chiral protein molecule.[158] As shown in Figure 3-3, the 3-dimensional nature of the protein pocket selects both the substrate or substrates that may interact

with the active metal site. Olefins that have substituents that are large cannot pass through the protein

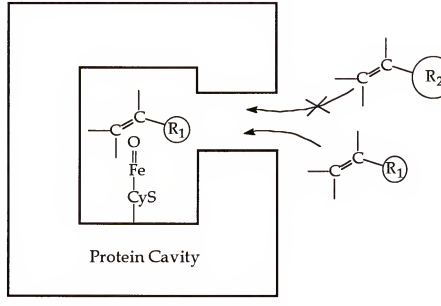

Figure 3-3.[164] Depiction of the protein pocket in cytochrome P-450.

cavity, while olefins with smaller substituents are able to access the active metal site. The protein exhibits shape selectivity in this manner. Chirality is induced by the chiral substituents within the protein structure in these heme systems.

In the oxygenase enzymes, such as cytochrome P-450, a metal-oxo species is formed by molecular oxygen. The general scheme in the metal-oxo formation is shown in Figure 3-4. The essential features of this type of system follows the sequence of substrate binding in a protein pocket, electron transfer, oxygen binding, protonation to yield the high valent metal-oxo, and substrate oxidation to complete the cycle. The biological pathway may be shunted by using oxidants that form the high valent metal-oxo without going though the electron tranfer, oxygen binding, and protonation steps.

Attempts to understand and mimic cytochrome P-450 led to the development of various porphyrin-based transition metal catalysts.[159-163] The porphyrins give each catalyst steric bulk around the active metal center and functions as the shape selective component of the catalyst. These porphyrin systems utilize various oxidants such as alkylhydroperoxides, percarboxylic acids, iodosylbenzene, and hypochlorite, to form a high valent metal-oxo species that subsequently transfers the oxygen to an olefin.[165,166] Many mechanistic studies have been done on these systems, but the exact mechanism of epoxidation catalyzed by metalloporphyrins is still controversial.[167-171] These studies address shape selectivity and the mechanisms involved in the epoxidations, but none addresses enantioselectivity.

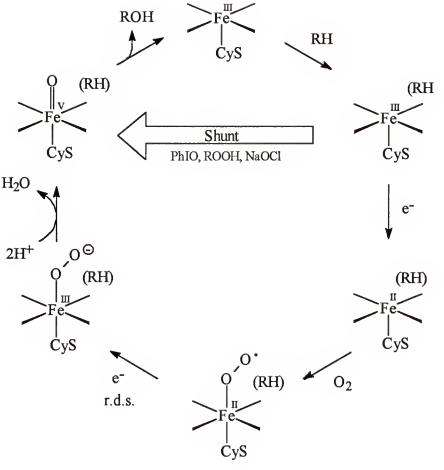

Figure 3-4.[164] Oxidation pathway with cytochrome P-450.

Enantioselective Epoxidations

The difficulty in enantioselective epoxidation of alkenes is the control of the olefin approach to the active metal site. With functionalized olefins, this problem is solved by the use of functional groups that ligate the olefin to the catalyst.

The most well known system in the epoxidation of functionalized olefins is the Sharpless epoxidation of allylic alcohols. This system employs a titanium tartrate catalyst and tertiary butylhydroperoxide that effectively facilitates enantioselective epoxidations in methylene chloride at -20°C.[172-174] In this system, chiral tartrates complex with titanium isopropoxide to give a chiral dimer complex with C_2 symmetry.[173] The alcohol moiety of the allylic alcohol substrates bind to the Ti. The olefin is orientated in a specific manner by the chiral tartrate ligands so subsequent oxygen transfer by a bound tertiary butylhydroperoxide preferentially yields one epoxide isomer over the other.[175] This system has a major limitation in being effective only for the enantioselective epoxidation of functionalized olefins. When a nonfunctionalized olefin is oxidized with the Sharpless catalyst, high enantioselectivity is generally not observed.

The greater challenge is to design an epoxidation catalyst that can facilitate enantioselective epoxidations of nonfunctionalized olefins. This type of system can accommodate a much larger range of olefins that can be subject to enantioselective epoxidations. The major difference between this type of system

and the Sharpless system is chiral recognition must occur solely through nonbonding interactions.

There has been an enormous amount of work in developing chiral metalloporphyrins for use in enantioselective epoxidations of nonfunctionalized olefins. Chiral porphyrins have been prepared in three ways.[164] The most common approach was pioneered by Groves and Meyers (Figure 3-5a), which introduces chiral acyl groups to pre-existing porphyrin structures.[176] The method used by O'Malley and Kodadek condenses chiral aldehydes with pyrrole to form the corresponding chiral porphyrin.[177] The method by Inoue and coworkers involves the synthesis of a racemic mixture and the separation of the enantiomers by HPLC using a chiral stationary phase.[178]

Chiral porphyrins can be divided into three structural types. Type I systems are chiral "picket fence" porphyrins having two or four chiral "pickets" above and below the porphyrin structure. Type II systems are porphyrins with chiral basket handles that connect diagonal positions with one or both faces of the macrocycle. Type III systems have adjacent meso positions that are connected by chiral straps. These straps may or may not be bridged by another strap that connects the chiral handles.

Type IA porphyrins with two "pickets" have not been especially effective as enantioselective epoxidation catalysts, achieving only up to 33% enantiomeric excess.[176,177] Type IB porphyrins with four "pickets" have much greater success in asymmetric epoxidations, achieving enantiomeric excesses of up to 76%.[179-181]

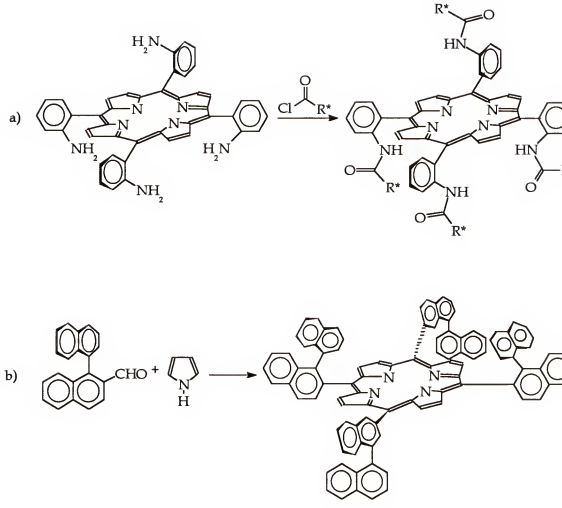

Figure 3-5.[176,177] **Various methods of preparation of chiral porphyrins.**

Type IB systems have two additional chiral centers that are more effective in inducing asymmetry from the catalyst to the substrate.

The use of Type II porphyrin systems generally lead to higher enantioselectivities than Type I systems. The bridged systems are especially effective since the bridge helps in positioning the chiral units closer to the active site. The best result in the oxidation of cis-β-methylstyrene with a Type IA system gave 40% enantiomeric excess, while a similar Type II system gave 88% enantiomeric excess.[176,182]

The Type III systems are among the most effective enantioselective catalysts derived from metalloporphyrins. There are various subclasses within the Type III family, such as the Type IIIA and Type IIIB, which include the "twin coronet" porphyrins and the Type IIIC and Type IIID that includes the threitol-strapped porphyrins.[183-186] In each type of Type III system, enantioselective olefin epoxidations require the chiral groups to be far enough from the active site to permit the substrate to access the metal site, but must be close enough to generate high enantioselectivities. A happy medium must be met in the design of an effective metalloporphyrin to be used in asymmetric epoxidations, and, generally, it is not an easy task.

The great importance of enantioselective epoxidation has led to the development of systems other than the biologically modeled metalloporphyrins. A significant impact has been made by systems based on chiral salen ligands, which are salicylidene ethylenediamine derivatives. These salen ligands bind to

transition metals in a rigid square planar configuration, similar to the porphyrin systems. It is known that achiral Mn(III) salen complexes catalyze the epoxidation of olefins, and chiral analogs of this catalyst are good candidates for enantioselective epoxidations.[187] Chiral transition metal complexes with salen have a distinct advantage over their porphyrin counterparts, where the salen ligand contains two chiral carbons that are two bond lengths away from the metal center. In contrast, porphyrins have their chiral constituents more than four bonds away. The close proximity of the chiral carbons in asymmetric salen complexes offers a very effective way for the substrate to be subject to chiral recognition.

The first reports of asymmetric catalytic epoxidation of olefins with manganese salen complexes were made by Jacobsen and co-workers.[188-191] These catalysts were synthesized by condensing salicylaldehyde with either a chiral 1,2-diamino-1,2-diphenylethane or a chiral trans-1,2-diaminocyclohexane, and then complexing it with manganese to form the corresponding chiral Mn(III)salen complex, as shown in Figure 3-6. These catalysts have been used in the enantioselective epoxidations of a variety of olefins, including conjugated dienes and enynes, chromenes, trisubstituted olefins, cinnamate esters, and conjugated polyenes, giving enantiomeric excesses between 41% and 98%.[192-197] Since the development of these catalysts, there have been over one hundred

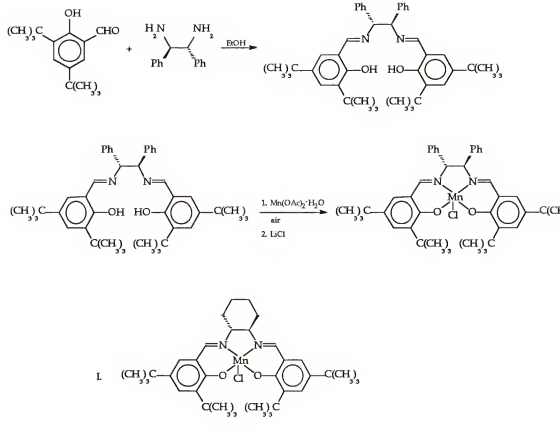

Figure 3-6.[190,191] Preparation of asymmetric Mn(III)salen complexes derived from a chiral diphenyl ethylene diamine.

derivatives of this catalyst synthesized and studied in the enantioselective epoxidation of nonfunctionalized olefins.

In this chapter, we synthesize a variety of chiral Schiff base complexes derived from amino acids. Amino acids are an inexpensive source of chirality and they are readily available from commercial sources. These complexes were screened in a variety of epoxidation reaction conditions, and then evaluated for their ability to induceenantioselective epoxidations. These catalyst systems have not been previously utilized in enantioselective epoxidations. Styrene was the model compound since it has one prochiral center, is inexpensive, and is readily available.

Experimental

Reagents and Equipment

Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification. All solvents were distilled and stored over 4A molecular sieves before use. Gas chromatographic analyses on volatile products and reactants were carried out using a Hewlett Packard model 5890 gas chromatograph equipped with a Hewlett Packard 50+ column (crosslinked 50% phenyl methyl - 30m x 0.53mm x 1.0μm film thickness), helium as the carrier gas, a flame ionization detector, and a Hewlett Packard 3396 Series II integrator. The temperature program used in all GC analyses was an initial

temperature of 90°C for 4.5 minutes, followed by a ramp at 35°C/min to 200°C, and maintaining 200°C for 5 minutes. Substrates and products were identified against known standards. Calibration curves were used to relate peak areas to the number of moles of products and reactants. Decane was used as an internal standard in all oxidation reactions. Column chromatography and flash chromatography was performed using 60Å, 200-425 mesh silica packed in glass columns, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were obtained on a Varian VXR-300 spectrometer interfaced to a Sun Sparc Station. Infrared spectroscopy was performed on a Nicolet 5PC equipped with a 1MW HeNe laser and Nicolet PCIR software (version 3.2). UV/Vis spectroscopy was performed on a Perkin Elmer Lambda 6 equipped with a deuterium lamp and Perkin Elmer Data Manager software. Elemental analyses data and mass spectra were performed by Spectral Services at the University of Florida.

Preparation of Salicylidene-L-Histidine

This procedure is a modification of a previous literature preparation.[192] Under an atmosphere of dry nitrogen, sodium hydroxide (0.3711g, 9.278 mmol) was dissolved in 30 mL of methanol. To this solution, L-histidine (1.44g, 9.28 mmol) was added, and the solution was stirred under reflux until dissolution was complete. The solution was then cooled in an ice bath to <5°C and salicylaldehyde (0.99 mL, 9.28 mmol) dissolved in 5 mL methanol was added with stirring. Immediately, the color of the solution changed from a pale yellow

to deep-lemon yellow. The reaction was allowed to go to completion by stirring for another 30 minutes at <5°C. The product was crystallized by excess diffusion of anhydrous diethyl ether into the solution under a dry nitrogen atmosphere. Rotary evaporation of the solvent left a deep-yellow crystalline solid. The product was recrystallized by dissolving in a minimum amount of hot methanol, and then recrystallized by diethyl ether. The yellow solid was filtered, washed with diethyl ether and dried under vacuum for 24 hours. Yield 50-60%; IR data: (2700-3400 cm^{-1}, 1632 cm^{-1}, 1600 cm^{-1}, 1405 cm^{-1})

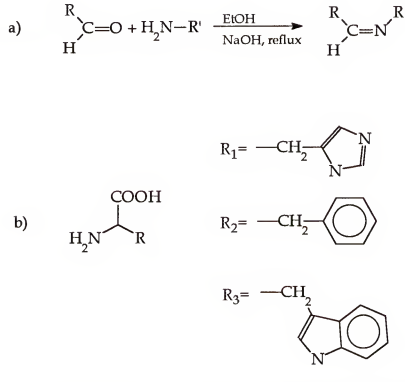

Figure 3-7. a) Preparation of salicylidene amino acid ligands, b) amino acids used.

Preparation of Salicylidene L-Tryptophan and Salicylidene L-Phenylalanine

Salicylidene L-tryptophan was prepared following the procedure described in the synthesis of salicylidene L-histidine, but 1.99g (9.28 mmol) of L-tryptophan was used in place of L-histidine. Salicylidene L-phenylalanine was prepared following the procedure described in the synthesis of salicylidene L-histidine, but 1.53g (9.28 mmol) of L-phenylalanine was used in place of L-histidine. Found for sal-L-phe: Yield 45-60%; IR: (2700-3400 cm^{-1}, 1634 cm^{-1}, 1604 cm^{-1}). Found for sal-L-try: Yield 46%; IR data: (2700-3400 cm^{-1}, 1625 cm^{-1}, 1583 cm^{-1}, 1408 cm^{-1}).

Preparation of Manganese Salicylidene L-Amino Acid (Mn^{II}sal-L-aa)

Two methods of preparing manganese salicylidene L-amino acid complexes were investigated.

1) In a three necked flask equipped with a condenser, 1.86 mmol of the appropriate salicylidene L-amino acid (sal-L-phe, sal-L-try, or sal-L-his) was dissolved in 15 mL methanol while stirring under a dry nitrogen atmosphere at room temperature. A separate solution was prepared, consisting of 0.935 mmol $Mn(OAc)_2 4H_2O$ dissolved in 15 mL absolute ethanol and purged with nitrogen at room temperature before transferring to an addition funnel. The $Mn(OAc)_2 4H_2O$ solution was slowly added to the refluxing salicylidene L-amino acid solution at a rate of about 10 drops per minute. The pale yellow solution turned brown after several minutes of reflux, and was allowed to reflux for 1.5

hours. When the solution was cooled to <5°C in an ice bath, a brown precipitate formed. The precipitate was filtered, washed with cold methanol, and dried under vacuum at room temperature. Yield <15%.

2) Since method 1) gave poor yields, the complexes were synthesized by a modified literature preparation.[193] The appropriate L-amino acid (5.00 mmol) was dissolved in 30 mL absolute ethanol under a nitrogen atmosphere. Upon dropwise addition of salicylaldehyde (0.544 mL, 5.00 mmol), the colorless solution became yellow. The solution was refluxed for 10 minutes. 30 mL of an ethanolic solution containing $Mn(OAc)_2{\cdot}4H_2O$ (5.00 mmol) was added dropwise at a rate that maintained uninterrupted reflux. A tan colored precipitate formed immediately, and the solution was refluxed for another 3 hours. The precipitate was filtered, washed with cold absolute ethanol, and dried under vacuum at room temperature for 24 hours. A 50-70% yield was obtained.

Analyses: Found for $Mn_2(sal\text{-}L\text{-}phe)_2{\cdot}3H_2O$: C, 54.48%; H, 4.74%; and N, 3.77%; IR data: (1635 cm^{-1}, 1582 cm^{-1}, 1417 cm^{-1}, 1343 cm^{-1}). Calculated: C, 55.03%, H, 4.62%, and N, 4.01%. Found for $Mn_2(sal\text{-}L\text{-}try)_2{\cdot}3H_2O$: C, 55.46%; H, 4.04%; and N, 6.80. Calculated: C, 55.68%; H, 4.11; and N, 7.24%; IR data: (1621 cm^{-1}, 1597 cm^{-1}, 1420 cm^{-1}, 1296 cm^{-1}). Found for $Mn_2(sal\text{-}L\text{-}his)_2{\cdot}3H_2O$: C, 42.42%;, H, 4.00; and N, 11.29; IR data: (1363 cm^{-1}, 1602 cm^{-1}, 1390 cm^{-1}, 1302 cm^{-1}). Calculated: C, 45.88%; H, 4.45%, and N, 12.35%.

Preparation of Mn^{III}(sal-L-his)

The same procedure for the synthesis of Mn^{II}(sal-L-his) was used except the reaction mixture was stirred under an air atmosphere after the addition of $Mn(OAc)_2 \cdot 4H_2O$. The solution turned a dark brown color within minutes of the addition of $Mn(OAc)_2 \cdot 4H_2O$. After stirring overnight, the solution was cooled in an ice bath to <5°C and the dark brown precipitate was filtered, wash with cold absolute ethanol, and dried at room temperature for 24 hours. Analysis: Found for Mn_2(sal-L-his)$_2(CH_3COO)_2$: C, 41.47%; H, 4.15%; and N, 11.11%. Calculated: C, 41.71%, H, 3.75%, and N, 10.42%.

Preparation of a Schiff Base of L-Amino Acid and Phthalic Dicarboxaldehyde

Sodium hydroxide (0.167g, 4.18 mmol) was dissolved in 20 mL methanol and stirred under nitrogen. L-amino acid (4.18 mmol) was added and heated until dissolution was complete. A separate solution of phthalic dicarboxaldehyde (2.09 mmol) in methanol was also prepared. Both solutions were cooled to <5°C, and the phthalic dicarboxaldehyde solution was added dropwise to the solution containing L-amino acid. The solution was allowed to stir overnight at room temperature and resulted in a yellow-brown solution. The product was crystallized by slow diffusion of excess diethyl ether into the solution, and resulted in a orange/brown precipitate. The solid was filtered, washed with diethyl ether, and dried under vacuum for 24 hours. The three

analogs synthesized were phthalic diimino-L-histidine (PDH), phthalic diimino-L-tryptophan (PDT), and phthalic diimino-L-phenylalanine (PDP).

Analyses: Found for PDH: C, 50.67%; H, 4.71%; and N, 15.71%. Calculated for PDH: C, 58.82; H, 4.94%; and N, 20.58%. Found for PDP: C, 74.65%; H, 4.92%; and N, 6.22%. Calculated for PDP: C, 72.88%; H, 5.65%; and N, 6.54%. Found for PDT: C, 71.90%; H, 5.92%; and N, 10.92%. Calculated for PDT: C, 71.13%; H, 5.17%; and N, 11.06%.

Preparation of a Manganese Complex of Phthalic Diimino L-Histidine

In a round bottom flask, phthalic diimino-L-histidine (0.094g, 0.23 mmol) was dissolved in 100 mL of absolute ethanol. The solution was brought to reflux before a 10 mL solution of $Mn(OAc)_2{\cdot}4H_2O$ (0.058g, 0.23 mmol) in absolute ethanol was added dropwise at a rate in which the reflux was not interrupted. The funnel was rinsed with absolute ethanol, and the solution was allowed to reflux for another 2 hours. The cloudy suspension that resulted was cooled in an ice bath to <5°C. The olive green precipitate was collected by filtration, and washed with three 10 mL aliqouts of cold absolute ethanol, and dried under vacuum for 24 hours at room temperature. Yield, 57.8%. Analyses: Found for $Mn^{III}PDH(OAc){\cdot}H_2O$: C, 44.36%; H, 4.19%; and N, 14.30%. Calculated for $MnPDH(OAc){\cdot}H_2O$: C, 44.29%; H, 4.07%; and N, 14.76%.

General Procedure for Epoxidation of Styrene With Tertiary Butylhydroperoxide

The appropriate catalyst (0.11 mmol) was added to a solution of styrene (15.0 mL, 99% pure, 130 mmol), tertiary butylhydroperoxide (90% pure, 15 mL, 130 mmol) and decane (0.1 mL, 0.513 mmol) in the appropriate solvent (15.0 mL). The solvents and catalysts used will be discussed section of this chapter. The resulting brown solution was stirred at room temperature. Reactant consumption and reaction products were periodically monitored and quantified by GC. The moles of each reactant and known product were determined by calibration curves for each compound. All reactions were stopped after 24 hours, unless stated otherwise. The reaction products were separated by flash chromatography (silica gel, hexanes/diethyl ether 80:20, v/v) to afford a fraction containing styrene oxide. Analysis of styrene oxide: ^{1}H NMR ($CDCl_3$) δ 2.81 (dd, J_1 = 5.4Hz, J_2 = 3.0Hz, 1H), δ 3.15 (dd, J_1 = 5.4Hz, J_2 = 1.5Hz, 1H), δ 3.87 (dd, J_1 = 4.2Hz, J_2 = 1.5Hz, 1H), δ 7.33 (m, 5H).

General Procedure For the Epoxidation of Styrene With Hydrogen Peroxide

The appropriate catalyst (0.11 mmol) was added to a solution of styrene (2 mL, 99% pure, 17.3 mmol), 35% hydrogen peroxide (10 mL, 113 mmol) and decane (0.1 mL, 0.513 mmol) in the appropriate solvent (15.0 mL). The solvents and catalysts used are discussed in the discussion of this chapter. Some reactions were buffered by the addition of sodium carbonate (0.53g, 6.39 mmol) and sodium bicarbonate (0.42g, 6.39 mmol) to the solution before the addition of the

catalyst. The resulting brown solution was stirred at room temperature. Reactant consumption and reaction products were periodically monitored and quantified by GC. For reaction solutions that resulted in two phases, GC samples were taken from the organic layer. The moles of each reactant and known products were determined using a calibration curve for each compound. All reactions were stopped after 24 hours, unless stated otherwise. The reaction products were separated by flash chromatography (silica gel, hexanes/diethyl ether 80:20, v/v) to afford a fraction containing styrene oxide. Analysis of styrene oxide: ^{1}H NMR ($CDCl_3$) δ 2.81 (dd, J_1 = 5.4Hz, J_2 = 3.0Hz, 1H), δ 3.15 (dd, J_1 = 5.4Hz, J_2 = 1.5Hz, 1H), δ 3.87 (dd, J_1 = 4.2Hz, J_2 = 1.5Hz, 1H), δ 7.33 (m, 5H).

General Procedure For the Epoxidation of Styrene Using Oxygen and Aldehydes

The appropriate catalyst (0.063 mmol) was added to a solution of styrene (0.344mL, 3.00 mmol), decane (0.1 mL, 0.513 mmol), and methylene chloride (5 mL) in a 250 mL pressure bottle. The reactor was stoppered with a pressure head and pressurized with 50 psig of air or oxygen. The reaction was allowed to stir at room temperature. Reactant consumption and reaction products were periodically monitored and quantified by GC. The moles of each reactant and known product were determined using a calibration curve for each compound. All reactions were stopped after 24 hours. The reaction products were separated by flash chromatography (silica gel, hexanes/diethyl ether 80:20, v/v) to afford a

fraction containing styrene oxide. Analysis of styrene oxide: ^{1}H NMR ($CDCl_3$) δ 2.81 (dd, J_1 = 5.4Hz, J_2 = 3.0Hz, 1H), δ 3.15 (dd, J_1 = 5.4Hz, J_2 = 1.5Hz, 1H), δ 3.87 (dd, J_1 = 4.2Hz, J_2 = 1.5Hz, 1H), δ 7.33 (m, 5H).

General Procedure to Determine Enantiomeric Excess of Styrene Oxide

A sample of the isolated styrene oxide (0.10 mL) was placed in an NMR tube along with tetramethylsilane (0.10 mL), and dissolved in $CDCl_3$ (0.5 mL). An initial ^{1}H NMR spectrum was taken before 0.10 mL aliquots of a $CDCl_3$ solution containing tris-[3-(heptafluorpropylhydroxymethylene)-(+)-camphorato] europium(III) derivative, [Eu(hfc)$_3$] were added to the NMR sample tube. The ^{1}H NMR spectra were monitored for the shift in the doublet of doublets peak at δ 3.15. When the appropriate amount of the Eu(hfc)$_3$ solution was added, the peak would shift downfield to approximately δ 3.7 and be split into a doublet of triplets. The integration of these two peaks was used to calculate the enantiomeric excess (e.e.) by Equation 3-1:

$$e.e = \frac{\text{(integration of Peak 1) - (integration of Peak 2) x 100}}{\text{(integration of Peak 1) + (integration of Peak 2)}} \qquad (3\text{-}1)$$

Results and Discussion

Styrene Epoxidation

The first objective was to find suitable reaction conditions to effectively carry out the epoxidation reactions. After a good system for our catalysts was found, enantioselective studies were done. Styrene was used as the model substrate in the epoxidation reactions since it has one prochiral carbon, is inexpensive, and is readily available. Figure 3-8 is a scheme for the stereochemical outcome depending on the approach of an oxidant to the double bond. The backside approach of an oxidant gives the R-configuration on the benzylic carbon, while the frontal approach gives the S-configuration on the benzylic carbon. Our major goal was to find a catalytic system that exhibits enantioselectivity with promising systems being optimized in the future.

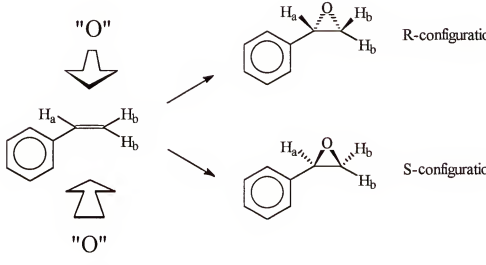

Figure 3-8. Depiction of oxidant approach to styrene and the stereochemical outcomes.

In the initial screening of the activity of our catalysts, epoxidation reactions were run using acetonitrile as the solvent. There have been accounts of other epoxidation reactions that gave good yields and selectivity with this solvent making it a rational choice as the solvent.[194-197] Tertiary butylhydroperoxide, a common oxidant used in olefin epoxidation, was used in screening reactions.

Investigations began with styrene epoxidations using the in-situ generated cobalt, copper, and manganese salicylidene L-phenylalanine complexes. The results are tabulated in Table 3-1. The Co(sal-L-phe)-catalyzed styrene epoxidation showed 56.7% consumption of styrene, but selectivity was poor at 2.0%. Other unidentified products were also observed. Cobalt has two stable oxidation states separated by one (Co^{II} and Co^{III}) and is expected to decompose TBHP by the Haber Weiss decomposition pathway. Benzaldehyde (6.17 mmol), phenylacetaldehyde (0.53 mmol), and acetophenone (1.76 mmol) were observed in significant amounts, indicating that other oxidation pathways occur. The Mn(sal-L-phe)-catalyzed reaction showed the highest consumption of styrene, although the selectivity was also poor (4.5%). Benzaldehyde (7.31 mmol), phenylacetaldehyde (1.07 mmol), and acetophenone (5.64 mmol) were observed products. Other unidentified products are also observed. In the absence of catalyst, no reaction was not observed.

Table 3-1. Transition metal salicylidene L-phenylalanine Catalyzed Styrene Epoxidation using Cobalt, Copper, and Manganese.

Catalyst	Time (hr)	Substrate Decrease	Epoxide Selectivity	B[b] (mmol)	PAA[c] (mmol)	AP[d] (mmol)
Co(sal-L-phe)	8	56.7 (73.7 mmol)	2.0% (1.47 mmol)	6.17	0.53	1.76
Cu(sal-L-phe)	8	0	0	0	0	0
Mn(sal-L-phe)	1	89.3% (116 mmol)	4.5% (5.22 mmol)	7.31	1.07	5.74
none	8	0	0	0	0	0

a) Calculated based on mmol of epoxide formed divided by the mmol of styrene consumed in the reaction.

b) Benzaldehyde yield

c) Phenylacetaldehyde yield

d) Acetophenone yield

Reaction Conditions:

Styrene:	130 mmol
TBHP:	130 mmol
Acetonitrile:	15.0 mL
Catalyst	0.11 mmol
Temperature:	ambient

Reactions were monitored by GC.

It is proposed that upon addition of the oxidant, the manganese(III) complex reacts with the oxidant to form an oxomanganese(V) complex via a Class III type reaction.[41] This is typical for the reaction of alkyl hydroperoxides with manganese(III) porphyrins to produce oxomanganese(V) complexes.[198,199] The reaction between manganese(III) and TBHP leads to either a homolytic oxidation or a heterolytic oxidation of the hydroperoxide, as shown in Figure 3-9. Homolytic oxidation corresponds to a one-electron transfer, which yields a tertiary butoxy radical and a manganese(IV) hydroxy complex. The reactivity of the tertiary butoxy radical with styrene accounts for the unidentified products in the

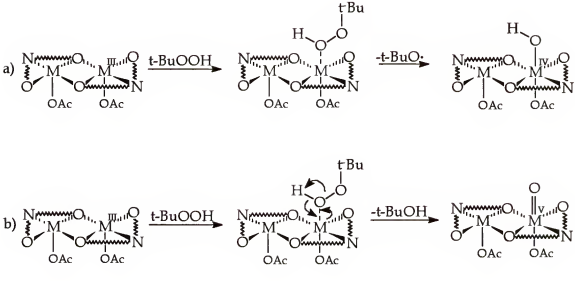

Figure 3-9.[200] a) homolytic and b) heterolytic oxidation of Mn(III) with TBHP.

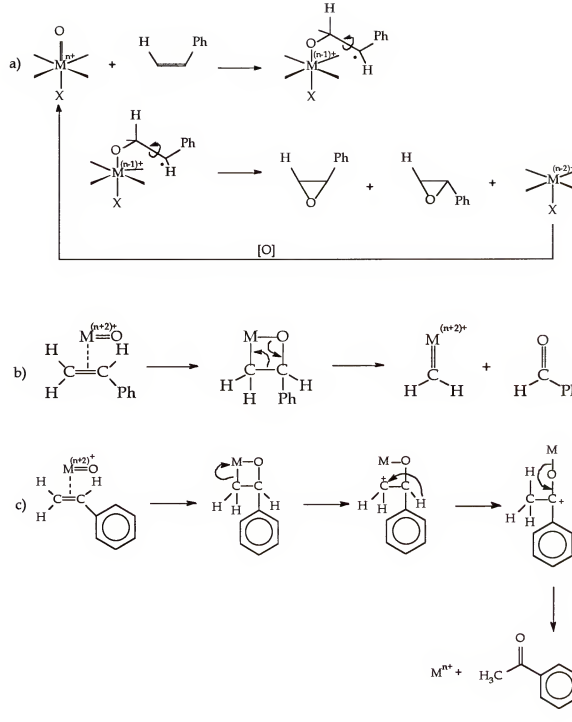

Figure 3-10. Proposed mechanisms of the formation of a) epoxide, b) benzaldehyde, and c) acetophenone.

reaction. Heterolytic cleavage is a two-electron transfer, which yields tertiary butylalcohol and an oxomanganese(V) complex. The oxomanganese(V) reacts with styrene by several oxidative pathways. The mechanisms shown in Figure 3-10 account for the formation of epoxide, benzaldehyde, and acetophenone via an oxomanganese(V) species.

The accepted mechanism for the formation of epoxides by an oxomanganese(V) species features the formation of a radical intermediate with a lifetime long enough to allow isomerization by rotation around the carbon-carbon bond.[200] Jacobsen and co-workers found that the epoxidation of cis-β-methylstyrene gave a mixture of cis and trans epoxides, showing a lack of stereospecificity that is in agreement with the proposed mechanism.[201] Although the reaction to form styrene oxide does not indicate stereospecificity, our epoxidations probably proceed by a similar mechanism. The epoxidation of cis-stilbene or trans-stilbene will be studied to investigate this mechanism.

The proposed mechanisms for forming benzaldehyde and acetophenone each undergo the same initial step where a metal-oxo forms a π-complex with the olefin and rearranges to a oxametallocyclobutane. Oxidative cleavage of the carbon-carbon bond leads to a metal carbene and benzaldehyde. A two-electron reduction of manganese(V) and a hydride shift leads to acetophenone.

The results for the catalyzed epoxidations of styrene by manganese salicylidene L-histidine [Mn(sal-L-his)] and manganese salicylidene L-phenylalanine

Table 3-2. Styrene epoxidation using Mn(sal-L-his) and Mn(sal-L-phe) and the effect of added pyridine to the reaction.

Catalyst	Pyridine	Styrene decrease	Epoxide Selectivity[a]	B[b] (mmol)	PAA[c] (mmol)	AP[d] (mmol)
Mn(sal-L-phe)	no	89.3% (116 mmol)	4.5% (5.22 mmol)	7.31	1.07	5.74
Mn(sal-L-his)	no	90.8% (118 mmol)	26.8% (31.6 mmol)	11.7	3.29	9.50
Mn(sal-L-phe)	yes	95.8% (125 mmol)	17.0% (21.3 mmol)	25.6	1.69	12.5
Mn(sal-L-his)	yes	75.3% (97.9 mmol)	13.4% (13.1 mmol)	8.73	0.829	7.71

a) Calculated based on mmol of epoxide formed divided by the mmol of styrene consumed in the reaction.

b) Benzaldehyde yield

c) Phenylacetaldehyde yield

d) Acetophenone yield

Reaction Conditions:

Styrene:	130 mmol
TBHP:	130 mmol
Catalyst	0.11 mmol
Temperature:	ambient
Reaction time:	1 hour

Reactions were monitored by GC.

[Mn(sal-L-phe)] are shown in Table 3-2. The consumption of styrene was about 90% for each reaction and occurred within 1 hour. Reaction times beyond 1 hour did not show a further decrease in styrene. Selectivity to epoxide was low in each case, but the reactivity of Mn(sal-L-his), which formed 31.6 mmol of epoxide (26.8% selectivity), was generally higher than for Mn(sal-L-phe), which gave 5.22 mmol (4.5% selectivity).

The addition of pyridine had contrasting effects for each catalyst system. The Mn(sal-L-his)-catalyzed reaction showed a decrease in reactivity in the presence of pyridine, shown by the decrease in styrene consumption from 116 mmol to 97.9 mmol. Selectivity to epoxide also decreased from 26.8% to 13.4%. These results are in contrast to the increase in reactivity for the Mn(sal-L-phe)-catalyzed epoxidation upon addition of pyridine. In this latter case, styrene consumption increased from 118 mmol to 125 mmol, while selectivity increased from 4.5% to 17.0%. These results may be rationalized by the effect of pyridine on μ-metal oxo dimerization.

The in-situ generation of the catalyst under an air atmosphere forms a brown manganese(III) complex with salicylidene L-amino acid. As shown in Figure 3-11, an equilibrium exists where the oxomanganese(V) complex and the manganese(III) complex couple to form a metal-oxo dimer. The resulting dimer has two manganese(IV) atoms bridged by an oxygen atom. This dimer is an inactive form of the complex since the oxygen atom cannot be effectively transferred to an olefin. Pyridine coordinates with the manganese(III)

complexes to form a coordinatively saturated manganese structure, as shown in Figure 3-11. The coordinatively saturated manganese(III) complex has no open sites to react with the oxomanganese(V) complex, and the formation of the μ-manganese(IV) oxo dimer is hindered. This leads to a higher concentration of oxomanganese(V) complexes able to transfer an oxygen atom to the olefin, and the oxidation process becomes more effective. The influences of pyridine on the styrene epoxidation catalyzed with Mn(sal-L-phe) can be rationalized this way. Mn^{III}(sal-L-phe) has one open coordination site that can bind pyridine, and the equilibrium in Figure 3-11 shifts to the right. As a consequence, reactivity is increased by the increase in the concentration of the oxomanganese(V) complex.

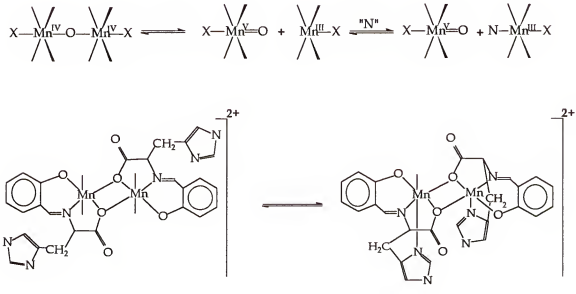

Figure 3-11. The effect of pyridine on μ-metal oxo dimerization.

The reactivity of Mn^{III}(sal-L-his) could not be rationalized in this way. The reactivity drops significantly in the presence of pyridine. It is proposed that the imidazole group of histidine coordinates to the open manganese(III) site and undergoes the equilibrium shown at the bottom of Figure 3-11. The addition of pyridine to Mn^{III}(sal-L-his) forms a higher number of coordinatively saturated Mn^{III}(sal-L-his), in which the sixth coordination site contains pyridine or imidazole. This inhibits the oxomanganese(V) formation, and lowers activity. The activity of Mn(sal-L-his) in the absence of pyridine is higher than the activity of Mn(sal-L-phe) in the presence of pyridine. Therefore, Mn(sal-L-his) was selected to screen the best epoxidation reaction conditions for enantioselective studies.

When the solvent was varied in the Mn(sal-L-his)-catalyzed styrene epoxidations, at least an 85% consumption of styrene was observed in all cases except for N-methylpyrrolidinone (NMP). The data is summarized in Table 3-3. The use of N-methylpyrrolidinone gave a low consumption of styrene of 28.2%, and a very low selectivity to epoxide. Consumption of oxidant may have occurred by its reaction with NMP, lowering the amount available for the oxidation of styrene.[202-204] Varying the solvent polarity from more polar to less polar resulted in an increase in the selectivity to epoxide.

Table 3-3. Solvent Variation and its Effects on Mn(sal-L-his) catalyzed styrene oxidation.

Solvent[a]	Styrene Decrease	Epoxide Selectivity[b]	B[c] (mmol)	PAA[d] (mmol)	AP[e] (mmol)
CH_3CN	89.3% (116 mmol)	4.5% (5.22 mmol)	7.31	1.07	5.74
NMP	28.2% (36.7 mmol)	7.2% (2.64 mmol)	5.01	0.629	0.419
t-BuOH	84.8% (110 mmol)	14.5% (16.0 mmol)	9.41	2.35	11.4
CH_2Cl_2	87.1% (113 mmol)	16.4% (18.6 mmol)	18.6	3.00	15.5
Toluene	90.0% (117 mmol)	20.6% (24.1 mmol)	31.3	3.39	16.1
Benzene	91.5% (119mmol)	33.7% (40.1 mmol)	10.0	4.51	14.9

a) 15.0 mL of solvent was used in each reaction.

b) Calculated based on mmol of epoxide formed divided by the mmol of styrene consumed in the reaction.

c) Benzaldehyde yield

d) Phenylacetaldehyde yield

e) Acetophenone yield

Reaction Conditions:

Styrene:	130 mmol
TBHP:	130 mmol
Catalyst	0.11 mmol
Temperature:	ambient
Reaction time:	3 hour

Reactions were monitored by GC.

A comparison of the styrene epoxidation catalyzed by the in-situ generated Mn(sal-L-his) and the isolated Mn(sal-L-his) was investigated. Table 3-4 shows identical activity in each of the epoxidations. It is reasonable to assume that the in-situ generation of Mn(sal-L-his) and the isolated Mn(sal-L-his) forms the same complex in solution, as reflected by the identical reactivity. Furthermore, the in-situ generation of the Mn(sal-L-his) led to a different reactivity than the

Table 3-4. Comparison of the in-situ generated Mn(sal-L-his) with the pre-formed Mn(sal-L-his) in styrene epoxidation.

Catalyst	Decrease in Styrene (%)	Selectivity to Epoxide (%)[a]
in-situ Mn(sal-L-his)	91.5% (119 mmol)	33.7% (40.1 mmol)
pre-formed Mn(sal-L-his)	92.0% (120 mmol)	30.2% ((36.2 mmol)
$Mn(OAc)_2 4H_2O$	49.2% (6.37 mmol)	3.9% (0.248 mmol)

a) Calculated based on mmol of epoxide formed divided by the mmol of styrene consumed in the reaction.

Reaction Conditions:

Styrene:	130 mmol
TBHP:	130 mmol
Benzene:	15.0 mL
Catalyst	0.11 mmol
Temperature:	ambient
Reaction time:	3 hour

Reactions were monitored by GC.

$Mn(OAc)_2{\cdot}4H_2O$ catalyzed reaction, which gave 49.2% consumption of styrene with 3.9% selectivity to epoxide. The in-situ generated Mn(sal-L-his) gave 94.5% styrene consumption with 30.2% selectivity to epoxide.

Three different oxidants were screened for styrene epoxidations using the Mn(sal-L-phe) catalyst with the results tabulated in Table 3-5. Sodium hypochlorite, which was available as commercial bleach, showed poor reactivity when used as the oxidant, but exhibited good epoxide selectivity. Although the substrate is only slightly soluble in aqueous solution, the use of 35% aqueous hydrogen peroxide exhibited a great improvement in reactivity. A hydrogen peroxide solution with a pH of 7.0 gave 98.9% substrate consumption with 22.4% selectivity. By comparison, a hydrogen peroxide solution with an initial pH of 4.0 gave nearly identical consumption of styrene, but selectivity decreased to 11.2%. In slightly acidic solution, the epoxide is more likely to undergo acid-catalyzed ring opening by the nucleophilic attack of the solvent. This was confirmed by the formation of the corresponding diol from the nucleophilic attack of water. Although the selectivity to epoxide is low with hydrogen peroxide, it was the most selective oxidant in this comparison study. Other contributions to the low selectivity of epoxide may come from the polymerization of styrene and styrene oxide.

The catalyzed epoxidation of styrene using a bicarbonate/carbonate buffer ensures that any acidic species will be absent in the reaction mixture, and the results of this investigation are tabulated in Table 3-6. Each reaction gave

Table 3-5. The effects of various oxidants on the Mn(sal-L-phe) catalyzed epoxidation of styrene.

Oxidant	Time (hr)	Substrate Decrease	Epoxide Selectivity[a]	B (mmol)	PAA (mmol)	AP (mmol)
NaOCl	4	5.30% (6.89 mmol)	66.9% (4.61 mmol)	1.32	1.65	1.25
TBHP	1	89.3% (116 mmol)	4.5% (5.22 mmol)	7.31	1.07	5.74
H_2O_2[b]	1	98.9% (129 mmol)	22.4% (28.8 mmol)	0.661	2.77	0
H_2O_2[c]	1	100% (130 mmol)	11.2% (14.6 mmol)	0.834	4.87	0

a) Calculated based on mmol of epoxide formed divided by the mmol of styrene consumed in the reaction.

b) Sodium hydroxide was added until the H_2O_2 solution was a pH of 7.0.

c) The H_2O_2 was used directly from the bottle.

Reaction Conditions:

Styrene:	130 mmol
Oxidant:	130 mmol
Acetonitrile:	15.0 mL
Catalyst	0.11 mmol
Temperature:	ambient
Reaction time:	variable

Reactions were monitored by GC

Table 3-6. Styrene Epoxidation using a Bicarbonate/Carbonate Buffer[a].

Catalyst	Styrene Conversion (%)	Epoxide Selectivity
Mn(sal-L-his)	83.7	67.0
Mn(sal-L-phe)	85.8	77.0
Mn(sal-L-try)	91.8	73.2
none	85.7	76.2

a) A 5% w/w sodium carbonate and 5% sodium bicarbonate buffer was used.

b) Calculated based on mmol of epoxide formed divided by the mmol of styrene consumed in the reaction.

c) The 15 mL 35% H_2O_2 was used directly from the bottle.

Reaction Conditions:

Styrene:	130 mmol
Oxidant:	130 mmol
Acetonitrile:	15.0 mL
Catalyst	0.11 mmol
Temperature:	ambient
Reaction time:	1 hour

Reactions were monitored by GC

nearly identical conversions of styrene (83.7% to 91.8%) and selectivity to epoxide (67.0% to 77.0%). However, the noncatalyzed reaction gave nearly identical results, with 85.7% styrene conversion with a 76.2% selectivity to epoxide. It can be concluded that the transition metal complexes are not involved in the oxidation process in the presence of this buffer. It is speculated that a reaction occurs between hydrogen peroxide and bicarbonate to form a percarbonate anion. Percarbonate has been demonstrated to be an effective oxidant, even in the absence of transition metal complexes.[205,206] Furthermore, epoxidations using percarbonate and perborate have been found to occur with olefins.[204,206-209] The mechanism of oxygen transfer from percarbonates occurs by the classical oxygen transfer mechanism found for most peroxyacids.[209,210]

Further investigation of the percarbonate-mediated epoxidation of styrene involved changing the solvent system from acetonitrile to methanol, since percarbonate epoxidations were generally done in methanol or ethanol.[206-209] No styrene consumption nor styrene oxide was observed by the change in solvent. It is concluded that percarbonate chemistry is not occurring in these buffered reactions. Styrene epoxidation occurs only in acetonitrile, which gives evidence that acetonitrile plays a major role in the reaction. It is proposed that the styrene epoxidation occurs by a peroxide formed by the reaction of acetonitrile and hydrogen peroxide. Epoxidation proceeds by the reaction of hydrogen peroxide and acetonitrile in basic solution to form peroxyimidic acid, as shown in Figure 3-12. Peroxyimidic acid has been shown to be a potent oxidant in olefin

epoxidations.[207] The carbonate ion abstracts a proton from hydrogen peroxide to form a hydroperoxy anion. The hydroperoxy anion undergoes nucleophilic attack on the nitrile carbon of acetonitrile to form the corresponding peroxyimidic acid. Peroxyimidic acid transfers oxygen atoms to olefins by the classical peroxy acid mechanism.[207]

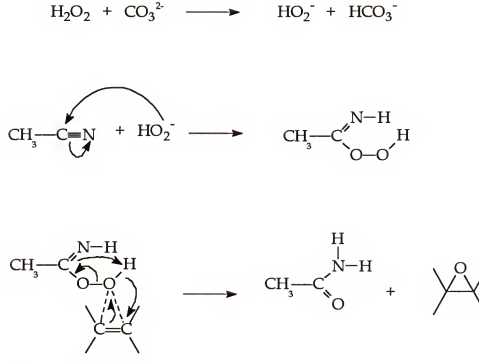

Figure 3-12. Formation of peroxyimidic acid and its function in epoxidation of olefins.

The epoxidation of styrene in the absence of catalyst gave identical epoxide yields and selectivity in the same time period as the epoxidation in the presence of a catalyst. Since Mn(sal-L-aa) is not involved in the oxidation reaction, it cannot mediate chiral recognition. It has been demonstrated,

however, that chiral peroxy acids can effectively facilitate enantioselective epoxidations of olefins.[211-214] Other systems must be investigated to increase selectivity of epoxide formation with our transition metal complexes to achieve enantioselectivity.

There have been accounts of epoxide synthesis using molecular oxygen and aldehydes in the absence of transition metal catalysts.[215] In addition, it was discovered that catalytic oxidation of olefins with molecular oxygen and aldehydes occurs with a variety of nickel and cobalt complexes giving high yields and selectivity.[216-221] Other studies with this type of system showed enantioselective epoxidation of a variety of chromenes. These systems were catalyzed by manganese complexes, achieving yields up to 88% with enantiomeric excesses of up to 77%. The similarity of our catalysts and these chiral manganese systems merits the investigation of styrene epoxidation with our systems. Furthermore, it is shown these systems are effective in the synthesis of epoxides that are acid sensitive, which makes it ideal to solve our acidity problem.

The results of styrene epoxidations using isobutyraldehyde in the presence of our Schiff base manganese complexes are tabulated in Table 3-7. In a recent study that screened a variety of aldehydes in the epoxidation of olefins using molecular oxygen, isobutyraldehyde gave among the highest epoxide yields and was chosen as the aldehyde. In each reaction, isobutyric acid was

Table 3-7. Manganese Salicylidene -L-amino acid Catalyzed Epoxidation of Styrene

Catalyst	Time (hours)	Decrease in Styrene (%)	Epoxide Yield (%)	Selectivity to Epoxide (%)[a]
none	24	50.6 (1.52 mmol)	2.7 (0.040 mmol)	5.3
Mn(salen')[b]	6	96.9 (2.91 mmol)	20.0 (0.582 mmol)	20.6
Mn(sal-L-phe)	6	100 (3.00 mmol)	11.5 (0.345 mmol)	11.5
Mn(sal-L-try)	6	83.0 (2.49 mmol)	4.9 (0.122 mmol)	5.9
Mn(sal-L-his)	6	100 (3.00 mmol)	62.5 (1.88 mmol)	62.5
Mn(Cl-sal-L-his)	2	99.8 (2.99 mmol)	33.7 (1.01 mmol)	33.7
Mn(MeO-sal-L-his)	6	98.3 (2.95 mmol)	34.1 (1.01 mmol)	34.7

a) Calculated based on mmol of epoxide formed divided by the mmol of styrene consumed in the reaction.

b) Jacobsen's catalyst (S,S)-(+)-N,N'-Bis(3,5-di-tert.-butylsalicylidene)-1,2-cyclohexane-diamino-manganese chloride

Reaction Conditions:

Styrene:	3 mmol
isobutyraldehyde:	9 mmol
O_2:	50 psi (39.3 mmol)
decane:	0.100 mL
Catalyst	0..063 mmol
Temperature:	ambient
Reaction time:	variable

Reactions were monitored by GC.

observed by GC analysis, making it reasonable to assume that the aldehyde behaves as an effective reductant by accepting one oxygen atom from molecular oxygen. The noncatalyzed reaction exhibited an induction period between 6 to 8 hours, during which no decrease in oxygen pressure was observed. After 24 hours, styrene was completely consumed, and along with styrene oxide, other oxidation products were observed (benzaldehyde: 14.7%; phenylacetaldehyde: trace; acetophenone: 3.6%). To date, there have been no reports in the literature of the noncatalyzed epoxidation of styrene using molecular oxygen and isobutyraldehyde. Changing the solvent from methylene chloride to methanol showed no consumption of styrene after 24 hours.

The use of our manganese salicylidene L-amino acid catalysts Mn(sal-L-aa)] with this reaction system eliminated the induction period, consumed styrene to a greater extent, and gave higher epoxide yields and selectivity. The Mn(sal-L-try) and Mn(sal-L-phe)-catalyzed reactions gave significant yields of benzaldehyde (up to 14%), phenylacetaldehyde (up to 8%), and acetophenone (up to 3%) and low epoxide yields of between 4.9% to 11.5%. Comparison between the noncatalyzed reaction with the use of Mn(sal-L-try) indicates that the latter reaction did not improve epoxide yield or selectivity, although the induction period was eliminated. In comparison, the Mn(salen) catalyzed reaction also eliminated the induction period, achieving higher epoxide yields of 20.0% with a selectivity of 20.6%.

The Mn(sal-L-his) catalyzed reaction showed the highest epoxide yield and selectivity. Derivatives of Mn(sal-L-his), which include manganese 5-chloro-salicylidene-L-histidine [Mn(Cl-sal-L-his)] and manganese 4,6-dimethoxy-salicylidene L-histidine [Mn(MeO-sal-L-his)], were also prepared and used in this reaction. As expected, the Mn(Cl-sal-L-his) catalyzed reaction consumed all the styrene at a higher rate.

Since the epoxidation of olefins with manganese complexes generally involves a metal-oxo species, it is assumed that a metal oxo species is generated in our system by molecular oxygen in the presence of aldehydes. The electron withdrawing chloro substituent makes the metal center more electron deficient and favors the nucleophilic attack of the olefinic double bond with the metal-oxo. In comparison, the Mn(MeO-sal-L-his) catalyzed reaction gave nearly identical epoxide yields and selectivity, but more time was required to achieve this. This may be attributed to the electron donating methoxy substituents, which makes the metal-oxo more electron rich and slows down nucleophilic attack of the olefin on the metal-oxo.

Enantioselective Epoxidation of Styrene

The yields and selectivities of epoxide in the styrene epoxidation reactions using molecular oxygen and isobutyraldehyde were the best of the systems studied. Enantioselectivity studies using this system were evaluated by NMR experiments. The addition of $Eu(hfc)_3$ to styrene split the benzylic hydrogen

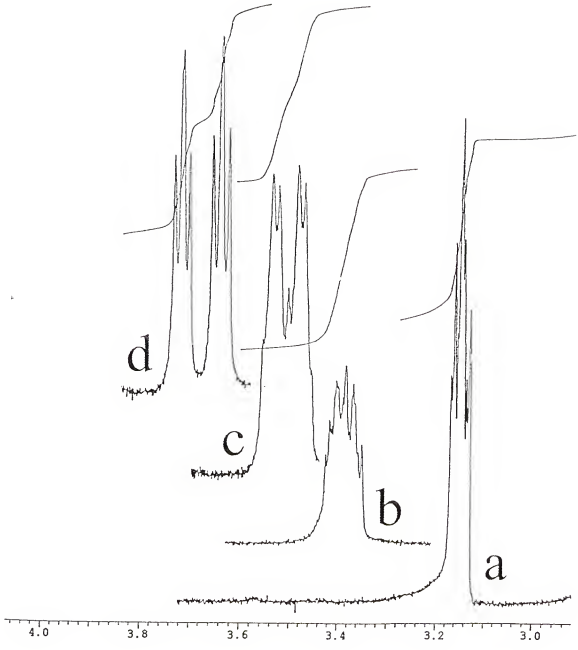

Figure 3-13. The ^{1}H NMR shift and splitting of the benzylic hydrogen upon addition of Eu(hfc)$_3$.

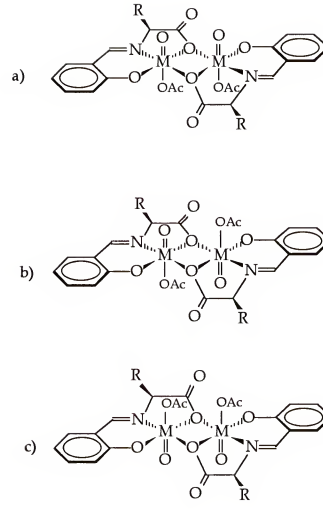

Figure 3-14. Possible orientations of the oxo group of Mn(sal-L-aa).

signal of styrene oxide in the ^1H spectra and enantiomeric excesses were calculated using Equation 3-1. The spectra obtained from a typical ^1H NMR experiment is shown in Figure 3-13.

It has been reported that manganese N-salicylidene amino acid complexes are dimeric structures with low symmetry, octahedral configurations.[222] The proposed structures of the active species of Mn(sal-L-aa) are shown in Figure 3-14. This structure shows the coordination of manganese to the phenolic oxygen, the imine nitrogen, and the carboxylate oxygen, which is shared by both metal atoms. The dimer has C_2 symmetry, with the chiral centers situated two bond lengths away from the transition metal center. Chiral recognition between the substrate and the catalyst is expected to be effective due to the close proximity of the chiral centers to the active metal site.

Table 3-8 summarizes the best results attained in the enantioselective epoxidation of styrene using manganese salicylidene L-amino acid complexes. The highest enantioselectivity was achieved by the methoxy-substituted manganese salicylidene L-histidine complex, giving 17.1% e.e.. It has been demonstrated by Jacobsen and co-workers that electron donating groups on the ligand leads to higher enantioselectivities.[223] In this literature study, it was suggested that the substituents cause changes in the electronic characteristics of the Mn-oxo bond in the active species. This results in varying degrees of substrate/ligand nonbonded interactions in the enantioselective transition states. As shown in the Mn(MeO-sal-L-his) catalyzed epoxidation, the electron

donating methoxy groups (EDG) on the catalyst decreases the rate of epoxidation. The catalyst functions as a milder oxidant and is expected to transfer oxygen to the double bond via a more reactant-like transition state resulting in greater nonbonding interactions.[222] This is in agreement with the higher enantiomeric excess found when comparing the use of this catalyst with both Mn(sal-L-his) and Mn(Cl-sal-L-his). In contrast, the electron-withdrawing chloro group in Mn(Cl-sal-L-his) increases the rate of epoxidation. The resulting catalyst is a stronger oxidant, and oxygen transfer occurs by a more product-like transition state. The consequence is greater separation between the substrate and catalyst, which is shown by a significantly lower enantiomeric excess of 4.0%.[222] As expected, the enantioselectivity using the nonsubstituted Mn(sal-L-his) falls between Mn(MeO-sal-L-his) and Mn(Cl-sal-L-his) since substituent effects are absent.

Table 3-8. Asymmetric Epoxidation of Styrene with Manganese Salicylidene L-amino acid catalysts.

Catalyst	Epoxide Yield	Enantiomeric Excess (%)[a]
Mn(sal-L-try)	4.9	5.9
Mn(sal-L-his)	62.5	8.3
Mn(Cl-L-his)	33.7	4.0
Mn(MeO-sal-L-his)	34.1	17.1
Mn(salen')[b]	20.0	42.3

a) Calculated by Equation 3-1.

b) Jacobsen's catalyst (S,S)-(+)-N,N'-Bis(3,5-di-tert.-butylsalicylidene)-1,2-cyclohexane-diamino-manganese chloride

Comparison of the enantioselectivities for the Mn(sal-L-aa) and the Mn(salen*) catalyzed reactions show that the Mn(sal-L-aa) catalysts are not as effective toward inducing chiral recognition. One inherent problem with the active species of each Mn(sal-L-aa) catalyst is they form various isomers, each exhibiting varying degrees of enantioselectivity. Figure 3-14 shows three different manganese-oxo isomers of Mn(sal-L-aa). The structure in Figure 3-14 a) is expected to be most effective towards inducing chiral recognition. The R-groups on the chiral center are cis to both oxo groups, and this configuration has the greatest influence on the orientation of incoming substrate molecules. The substrate must interact with the R-group as it approaches the metal center, and the favored orientation leads to asymmetric transfer of an oxygen atom. Oxygen transfer from both metal oxo groups to the substrate occurs in a chiral environment, and the highest possible enantioselectivity is achieved.

When the two oxo groups are trans to each other, as shown in Figure 3-14 b), only one R-group is able to interact with the substrate. The environment around the metal center has chiral influence for the R-group that is cis to the oxo group. This R-group interacts with the incoming substrate and the favored orientation leads to asymmetric transfer of an oxygen atom. At the other metal center, the R-group on the chiral center is trans to the oxo group and exhibits no substrate directing influences. Any substrate molecule that approaches this metal center will not be involved in asymmetric oxygen transfer.

No chiral recognition is expected for the isomer in which the oxo groups are cis to each other but trans to the R-groups, as shown in Figure 3-14 c). Incoming substrate molecules do not interact with any R-groups since both R groups are on the opposite side of the oxo group. Enantioselectivities are not expected with this isomer.

In all the Mn(sal-L-aa)-catalyzed styrene epoxidations, no discrimination among the formation of the three different isomers is expected. Each isomer has varying degrees of asymmetric induction and enantioselectivity suffers when all three are involved in oxygen transfer.

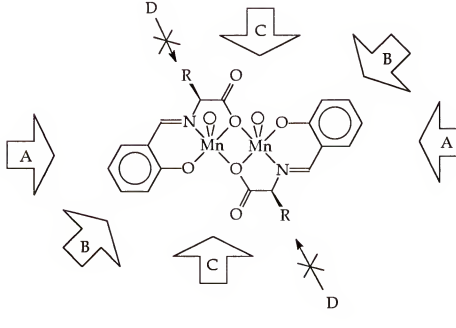

Figure 3-15. Various approaches to the metal center by the substrate.

A lack of steric bulk around the metal center of Mn(sal-L-aa) also contributes to the low enantioselectivities observed. Several approaches to the metal-oxo are possible, as indicated by arrows A, B, and C in Figure 3-15. The consequence is a decrease in asymmetric induction and a drop in enantioselectivity. The only discrimination is shown by arrow D, in which the R-group hinders the approach of the substrate to the metal center.

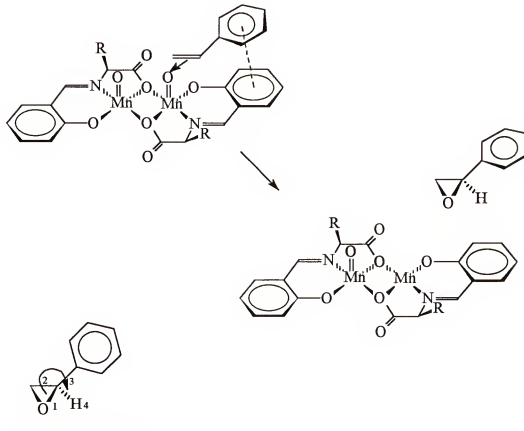

Figure 3-16. The approach of styrene to Mn(sal-L-his) that accounts for the formation of R-(+)-styrene oxide.

R-(+)-styrene oxide was the enantiomer produced in the Mn(sal-L-his)-catalyzed epoxidation reaction. This was indicated by the positive rotation of the polarimetric reading of a solution of the isolated styrene oxide in chloroform. To account for the formation of this enantiomer, the approach of styrene to the oxo-manganese(V) is shown in Figure 3-16. A side-on approach of the substrate to the metal center is proposed. π-Stacking of the phenyl rings is expected to occur between the substrate and the ligands. Rotation about the carbon-carbon single bond in styrene orientates the carbon-carbon double bond perpendicular to the metal oxo bond and subsequent oxygen transfer yields the corresponding R-(+)-styrene oxide.

It was successfully demonstrated that manganese salicylidene L-amino acid complexes induce enantioselective epoxidations. The novel use of these complexes in enantioselecitive epoxidations shows promise by utilizing inexpensive raw materials to synthesize these catalytic compounds. Although enantioselectivities were below 20% enantiomeric excess, substituting bulky groups onto the ligand may help increase enantioselectivity.

Conclusions

Novel applications of manganese salicylidene L-amino acid complexes in enantioselective epoxidations were successfully demonstrated. These complexes are derived from readily available and optically pure amino acids, and they are easily synthesized.

Screening various epoxidation reactions indicated that the epoxidation of styrene using molecular oxygen and isobutyraldehyde was the most effective system. Styrene oxidation using TBHP gave significant amounts of side products by other oxidation pathways. Styrene epoxidation using a carbonate/bicarbonate buffer and hydrogen peroxide in acetonitrile did not involve the transition metal catalysts, making it an ineffective enantioselective epoxidation system.

Enantioselective styrene epoxidations using Mn(sal-L-his) and its derivatives gave enantioselectivities of up to 17.1%. Substituting EWG and EDG onto the ligand affected enantioselectivities by changing the electronic characteristics of the catalyst. The low enantioselectivities were attributed to the lack of steric bulk around the metal center, which allowed various approaches of the substrate to the active site.

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BIOGRAPHICAL SKETCH

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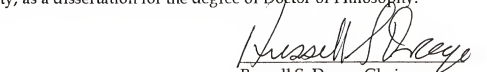

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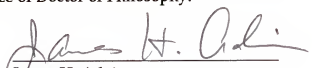

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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